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TRANSCRIPT OF PROCEEDINGS

NATIONAL INSTITUTES OF HEALTH

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NATIONAL MICROBIOLOGICAL INSTITUTE

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AD HOC COMMITTEE ON POLIOMYELITIS VACCINE

Bethesda, Maryland
April 30, 1955

Pages 1 thru 143

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[illegible]

[illegible] would like to publish my [illegible] to be [illegible] which I [illegible] people aren't [illegible] so, the committee [illegible] [illegible] discussion with the [illegible] [illegible] with the [illegible].

[illegible] hope to finish the [illegible] [illegible] noon, we'll, to [illegible], from [illegible] the morning we could finish this [illegible] [illegible] would hope that the committee could meet [illegible] lunch to [illegible] their findings and put in [illegible] their recommendation to our schools. [illegible] to everybody. Then [illegible] will [illegible] can go in [illegible] they want to [illegible].

later.

[illegible]

([illegible] follow[illegible] [illegible] representatives [illegible] contained as follows:)

DR. SHANNON: We quite frankly want [illegible] people we felt is his competent in this particular area, [illegible] having a record in my way would [illegible] person [illegible] really giving the best advice from the [illegible] of his experience. Then I would like to see it [illegible] because anything that is going to [illegible] I think we want to look at awfully carefully. [illegible] that is anybody looks that looking [illegible] things that we have will lead to very important [illegible] from the group, anything that will [illegible] to see the background of those recommendations [illegible]

[illegible]

[illegible] that there are two points [illegible] to discuss with the manufacturers' representatives this morning. The first point is as a result of our experience and knowledge, and recommendations [illegible] to be made in [illegible] requirements should be strengthened [illegible] there to make [illegible] tested [illegible] and the second point is [illegible] you what we might call safety experience. We feel that we would like to see [illegible] such material as the number of tests that you have made, or which are [illegible] that are rejected [illegible] so that we would have some idea of what the rejection rate is and on what it is based, as well as on the fatigue [illegible] come through as most [illegible] good fatigues.

Now I don't know what may be involved in this information, but some people have expressed the wonder that we need the total experience in order to determine [illegible] the best tests and also to help us decide what changes [illegible] are needed in the safety testing procedures.

Now these are the two points on which we [illegible] your advice and suggestions. Let me ask the rest [illegible] members of the Committee if I have presented the thing [illegible] they understand it, and then if this is so, do you [illegible] have any objection to taking a record of our [illegible]

[illegible]

Dr. [illegible] [illegible] record [illegible] [illegible] [illegible]

[illegible]

[illegible]

Dr. [illegible] I [illegible] I [illegible] to [illegible] the [illegible] of the [illegible] [illegible] to [illegible] for [illegible] [illegible] [illegible]

[illegible] [illegible] [illegible] [

[illegible]

[illegible]

[illegible]

[illegible] time [illegible]

[illegible] fall [illegible]

[illegible] that [illegible] the [illegible] line [illegible]

the safety test you all recall [illegible] meeting we had on it about a year ago. It seemed this might be a unusual affair. We came to Washington to discuss this in the spring each year, various [illegible] meeting. So we are calling this 'operation [illegible]'.

From the time of the first tissue culture safety testing was performed in Chicago, we perhaps were [illegible] in this and we felt that it was not adequate. We went on and [illegible] procedure we could, [illegible] bottles and other larger matrices that came along. We went into bottles, and finally I believe about a year ago in March this was discussed quite thoroughly and accepted by everyone, that we should go into bottles for safety tests.

Now soon after that there was a meeting and the question came up as to how long to keep the bottles or when the final readings should be made, and it was set [illegible] 14 day period. I believe at that meeting I made the statement that in our experience we had run some bottles longer than that, that not always could we eliminate bottles for a 28 day period, but we felt we should if we could, because we were having difficulties in [illegible] cost

[illegible]

[illegible] I [illegible]

[illegible] I [illegible]

[illegible] I [

[illegible] vaccine

[illegible] in the [illegible] of [illegible]

disease [illegible]. The [illegible] of [illegible] testing is of course

that one of the things we would like to get from you people

today is the relative sensitivity of these various tests

for virus.

DR. STIMPERT: As I said before, we have found no [illegible]

in monkeys in our laboratories. We have not had a positive

monkey.

DR. WORKMAN: That is at any time Fred?

DR. STIMPERT: Not at any time. Not a monkey in

our laboratory. I believe there was one either in your

laboratory or Dr. Salk's laboratory that involved one of your

lots earlier last year. Now I don't know whether that was

confirmed or not. But we have had none in our laboratory.

DR. WORKMAN: Very good. I was referring only

to your own test.

DR. MC LEAN: Dr. Murray has raised a point that I

think should be brought out. Tests are not done in our

laboratory until the final vaccine.

DR. SEBRELL: You don't run them concurrently?

You run the tissue test first.

DR. STIMPERT: On the strained pool.

DR. MC LEAN. And then repeat the tissue culture and do a

monkey test.

[illegible] -- [illegible] questions relative to [illegible] were [illegible] passed on in blood culture on the pooled sample positive culture from it had gone through this type of thing as an individual strain?

DR. SCHMIDT: I believe we have one.

DR. MC LEAN: We have had one. There is some question about the lot of tubes that were used. It was pooled up in tubes, and it is one of the cases that Jonas brought up the possibility -- we cannot rule out the possibility that type one virus is a contaminant in that fashion, too.

DR. SHANNON: That was one out of what?

DR. MC LEAN: About 50 to 55.

DR. SALK: Could you tell us how many flasks or bottles or tubes were in the denominator and how many in the numerator on any of these occasions when you detected virus on the 25th day or the 22nd day?

DR. MC LEAN: I can't remember that for all of them. Jonas. There are four, you notice. I will say that this does not include the entire experience. This is on some 500. The figure is indeterminate because it includes at least one that -- in other words, we have the 28 day test. We have a number in progress. But this data is only on the Parksdale farm unit lot, which is something over [illegible], in the neighborhood of 525, I think, 500. Out of these 4 that showed up in 28, I know that there is one in that [illegible]

[illegible] [illegible] [illegible] [

[illegible] I'd like to know what the

end.

DR. [illegible] Well, the reason I asked that, because the respiratory viruses and the question that you raised of the possible introduction from without, if the respiratory viruses are introduced in the transfers then is it possible that type 1, 2, or 3 polio could be introduced? The 20th day would give you the greatest possibility of getting that.

DR. MC LEAN: We also on the bottles we use for safety test will hold somewhere between 10 and 20 subcultures and carry them through as controlled, and that is quite helpful.

DR. [illegible]DIAN: Is it possible to repeat the 20 day positive and get a positive again?

DR. MC LEAN: We have on occasion had them repeated and had them show up in 14 days. We also had them repeated and didn't have any show up.

DR. SEBRELL: Any discussion further of Dr. Stimpert's presentation? We appreciate your discussion very much, Dr. Stimpert.

DR. FRANCIS: May I ask a question for information, Dr. Sebrell? Have you any suggestion in the regular fashion or do you have any more difficulty in type 1 or type 2 or type 3 virus?

DR. MC LEAN: I think the answer to that line is just before you, Dr. Francis. These represent about an equal

number of [illegible] lots of each, [illegible] have not shown no active virus before the 7th day, and those in the type 1 you notice are experimental lots. They are treated for shorter periods than we usually treat. In our routine production, in 11 to 14 days. We just never picked up anything in the first week.

DR. FRANCIS. These are experimental lots?

DR. MC LEAN: No, sir, the bottom four.

DR. SHANNON: Fred, could I ask a question? In retrospect when you find a strain with apparent contamination on the basis of these data and then you go back to look over the initial process can you see any correlation with what has happened to that batch as compared to other batches? In other words, inactivation occurs sometimes and other things.

DR. STIMPERT: Not in general.

DR. SHANNON: Have there been specific examples where you have been able to find correlation?

DR. STIMPERT: I don't think so, nothing we can point our finger out at.

DR. SHANNON: Then in retrospect when you find this you don't go back and say--

DR. STIMPERT: No, we always ask the question what has happened. I said to the people there "why don't you go on back"? They said "We have. We just can't find anything." You must remember, too, we are not doing one at a time. There

[illegible] the same [illegible] in the [illegible] pools, or the same formulation [illegible]. The difference is the material; that is, your raw material that you are using. That is your difference, and you move it by degree or whatever it is, concentration of viruses.

DR. SALK: How many lots or batches do you have going concurrently from which samples might be withdrawn on any given day?

DR. STIMPERT: It varies tremendously.

DR. MC LEAN: Much of that is a guess.

DR. SALK: In various stages of inactivation.

DR. FRANCIS: One point about this is interesting, and that is it seems that -- at least I haven't checked this completely, but certainly by inspection it doesn't appear that two or three viruses are found in the same lot of material.

DR. MC LEAN: These are not all avalents.

DR. FRANCIS: Under this circumstance then type 5 what about 5 and 9? They had the same number on two different days.

DR. MC LEAN: That is a repeat test. I will say that the way these are handled, these are treated for the standard period of time. If the test shows contamination they are returned to the incubator for two days and retested. In that particular case that lot showed up -- it is interesting

that the second one was [illegible]. - in other words the one that showed up in ten days was after an additional two days.

DR. SABIN: Could that be a single bottle positive or--

DR. MC LEAN: A single lot? I don't remember. Usually in most of these it is more than one bottle, but what is given here is the time the first bottle appeared. So I did not put the total number of bottles. I thought we should include that eventually. I will say as soon as we have confirmed virus we discontinue the test in most cases. We don't continue to run the thing out how many will go bad.

DR. SALK: In any one lot like P06183, how many bottles or flasks might be being inactivated, or does that number represent a single vessel?

DR. MC LEAN: Every one of these represents a single vessel.

DR. SALK: What size?

DR. MC LEAN: 60 liters.

DR. SALK: Do you happen to know what the time of exposure to formaldehyde was, or to heat, in these cases?

DR. MC LEAN: In most cases it would be 11 days. It went up for awhile to 14 days. I think it dropped back to 11. Some of these are 14 days, but the majority would be 11 day treatments. In the one case of 6, 7, which showed up again, that that would be 11 plus 2, or 13 days at 37.

DR. SMADEL: What happened to the lot then? Was it discarded?

DR. [illegible]: I [illegible] to [illegible] a period on [illegible] and then used.

DR. ENDERS: Is there any test, routine test made from the protein concentration of the pool?

DR. MC LEAN: Not of the individual strained pools. The final vaccine, we usually run a protein content.

DR. ENDERS: I was wondering possibly--

DR. MC LEAN: No, we have checked that. We haven't run it on all of these, but some that did come out, we compared them with ones that went through all right within the limit of variation in this thing.

DR. SALK: What about the point of interception of the base line in these lots and also the data showing rate of inactivation?

DR. MC LEAN: There was nothing out of line. We now have, as I said, data on some 800 strained pools. On all of these we do not have full bulk rate test. I reviewed those, and unfortunately there was not time to get all the stuff together in Detroit. There is no doubt that this is not a straight line. The curve hills off. We have paid very little attention to the bulk rate. We do it and we draw the line. It usually hits somewhere around 48 in 72 hours. We treat for a period that is in excess of that routine. We rely on our safety test to pick up the approximate 10 percent, is what it runs, of those that show up.

DR. [illegible]: Do you [illegible]?

DR. MC LEAN: We are running about 10 percent [illegible] pick up in our assay [illegible].

DR. [illegible]: What is of the individual strain?

DR. MC LEAN: Yes.

DR. ENDERS: You heat it at least three times as long as the curve was.

DR. MC LEAN: Yes, sir, heat it for 11 days, which is in excess of the longest period we have.

DR. SALK: How can you be sure if you do not have a first order process that you heat it long enough and why do you stop at 11 or 14 days?

DR. MC LEAN: Well, you have got to stop some time and we have set that because in our experience it has been a time that appears satisfactory.

DR. SALK: You got a certain percentage that turns out to be nonsatisfactory?

DR. MC LEAN: Yes.

DR. BODIAN: Do you get any comfort from knowing the inactivation curve?

DR. MC LEAN: No.

DR. BODIAN: For example, do you have any other way of knowing that something has been considerably wrong with the inactivation?

DR. MC LEAN: We do a 48 hour sample, which in our

experience will result in your accumulation of what I, or that general area.

DR. BODIAN: That is getting part of the curve.

DR. MC LEAN: That is getting the point that if you do draw a line it is the one you draw it through anyway. We do that only to assure ourselves that formin was actually added to the lot, or some gross error.

DR. BODIAN: You would never fail to test those two point, the original titer in the 48 hours?

DR. MC LEAN: That's right.

DR. SALK: Have you had any experience in which you tested samples between the 48 hour point and, let's say, the 11 or 14 day point, and if so, what experience have you had in the frequency of the rate which you have detectible virus, and is that any different at the beginning or end of that period?

DR. MC LEAN: It is hard to say. We have done in bottles saturations which indicate that they are something in the order of a hundred times as sensitive as our Hasa tubes. Therefore, we would expect to actually lower our titration. We have on several occasions taken samples at intervals say 2, 7, 5, 9 days. One encounters reversals in that. You get a clear test at 5 days, pick up positives at 7 days. It is our feeling that possibly there is some antagonism which may account for it or some other variation in the

physical characteristics of the virus proper. Now this is a hypothesis. We have no really basic evidence for it Certainly there is something that is true of other things besides formaldehyde, that to get that last trace amount it does seem to follow the curve one gets with the 99.999 percent.

DR. SALK: No, I would agree with this, but we are not plotting this arithmetically. We are plotting it logarithmatically, and two logs represent 99, 3 logs, 99.99. On a log plot you get one thing, but on an arithmetic thing you get the thing approaching the asimutope in different fashion. I say this for the edification of those that might not know the difference.

DR. MC LEAN: As I say, we accumulated all the data some time back, and part of it on the basis of six hour intervals we had to run from that way, and the log loss of virus -- in other words, subtracting the thing, it was a smooth curve with a belly. That was based on some 50 strained pools.

DR. SMADEL: Mr. Chairman, I don't think we are getting anywhere with this particular discussion. I mean the minimum requirements insist that it be done in such and such a manner. They have done them in such and such a manner. They have then gone on and inactivated for a period beyond that which the theoretical calculation would give them, and

that is [illegible] and I don't think that at this particular point although the subject is of considerable interest in fundamental virology, I don't see that it is going to help us very much in this immediate problem that we have facing us.

DR. STIMPERT: I was about to say we have given you the report. We have given you the benefit of some general ideas in it, and we have answered the questions, and I agree with Dr. Smadel if we get to a more technical discussion we ought to have it placed in the proper way to do that. Unless you gentlemen want to get into it, then we are perfectly willing to do it.

DR. SEBRELL: Well, I think we want to -- for me, I appreciate this discussion. I think the information, since I don't know anything of virology, is interesting, and the thing we want to know is as a result of this experience should we change the minimum requirements, and if so, how do we change them, and maybe we can't reach that decision today as to how they should be changed in detail, but perhaps you can as a result of today's discussion advise us whether further technical meetings are necessary and the directions in which you think perhaps they should be changed. You see, we had considerable discussion yesterday as to whether we should require more monkeys or not. I think what Dr. Stimpert said bears on this point quite directly and might help us

reach a decision about how we do or don't do this in question.

Is there anything further you want to add?

DR. STIMPERT: I would summarize, just add a little bit to the point you just mentioned in answer to your [illegible] question is there anything we would like to suggest. I did hint earlier that anything we can do to amplify, enhance the sensitivity or by more tests or by duplicate tests of the tissue culture, I think we should consider it. We think we have increased it by a number of bottles, by size of bottles, by amounts of material and so on as we have gone along, and we feel it has been beneficial to our feeling of confidence.

DR. SEBRELL: I would like to get clear whether I interpret what you have said correctly. I would assume from what you have said that you place more reliance on the tissue culture test than you do on the monkey?

DR. STIMPERT: Oh, no question.

DR. SHANNON: Fred, could I get one thing clear. I didn't get it. You gave a percentage of 10 percent positive safety test. What was that in relation to?

DR. MC LEAN: That is 50 out of 75, 100 plus.

DR. SHANNON: That is on the unpooled?

DR. MC LEAN: That is on the strained pool.

DR. SMADEL: So that in a given test with 5 bottles that is 45 cc's employed?

DR. MC LEAN: Five or more.

DR. [illegible]: It has gone up to 48.

DR. [illegible]: I think I should ask Dr. [illegible] one other question at this point bearing on yesterday's discussion. In discussing the inactivation curve yesterday there was some discussion about the number of points on the curve that might be required, and some people seemed to think that maybe we should require a minimum of 5 points on the curve in addition to the zero point in this inactivation curve. Now would you have any opinion as to whether this is desirable or not?

DR. STIMPERT: Well, I think if you want a curve I don't think we care how many points you put on it.

DR. MC LEAN: Well, we are doing, as I said, on one point -- the manufacturers met last winter some time and discussed this thing at some length, and it was my impression at that meeting that we agreed that the 48 hour point was the point that 99 percent of the time was the one that was used in determining the curve. Therefore, that was the most important point we could produce. This was my impression. I feel that this is ultimately just a guide to indicate that inactivation has occurred and that something has not gone wrong. We expect to get virus in a sample and we expect to have a titer within a certain range. If it is, I feel the test is all right. There have been no correlations between this data and the bulk rate data and the appearance of native virus

DR. SEBRELL: I think we had better move around to the next representative. I guess the next one is--

DR. MC ALLISTER: My name is McAllister.

DR. SEBRELL: He is going to speak for Wyeth.

DR. FRITZ: Yes.

DR. MC ALLISTER: I will summarize very quickly some of Wyeth's experience, and it goes as follows. First I better say that Wyeth in respect to the other drug companies, at least, for the first few months had a very rocky road. Between January and April of last year approximately 12 lots passed through the hands of the Wyeth Company, and using the 42 tissue culture safety tests, two of these failed, two out of the 12. However, when the bottle technique was applied a total of 6 out of12 failed. In this same group 3 failed on monkey.

When one goes back over this experience and tries to explain it, it is felt that perhaps the explanation does lie in, number one, inadequate time for some of the lots, and secondly, sampling deficiencies in the apparatus used.

From April last year until the present time the experience has changed. I would like to point out that right at that time we did seek the advice of Dr. Salk and Dr. Coriell who suggested several things be done, which I would like to outline just briefly.

First, the safety testing and inactivation was removed

from the production area. Secondly, all inactivation was one in 20 liter glass carboys, and each carboy was shaken daily on a shaker. Each second day the virus fluid in the carboy was passed over to a new carboy and all the sampling and apparatus removed and a stopper put on it, so that during the inactivation which in general is between 10 and 12 days there are a number of changes every second day. The fluid is passed over.

Now from April to date there have been 300 individual 20 liter carboy safety tests, of which 3 have failed.

DR. HAAS: What were the numbers again?

DR. MC ALLISTER: 300, 3 have failed. This is the experience from April last year to date approximately.

DR. BODIAN: Strained pools?

DR. MC ALLISTER: Strained pools, yes. Of the 300, 3 have failed. The explanation for these three eludes us. These three bottles were reinactivated and then passed.

DR. SHANNON: When you reviewed those three could you find anything in the data in retrospect you might have overlooked?

DR. MC ALLISTER: I will have to have some help from Mr. Coh. He tells me that the curves were drawn at zero, at 4 hour, and the next day two samples and the next day two samples. They were within the usual, which again is perhaps 60 and 70 hours for the most part. No, I don't think that one

could tell from that where the contamination is, in these three instances.

DR. BODIAN: Were these that failed in tissue culture tests of the single pools?

DR. MC ALLISTER: Yes. None have failed in monkeys since last April.

DR. SALK: To what extent, Dr. McAllister? How many bottles were innoculated with material from a 20 liter lot? You took a sample and innoculated in how many bottles and how many bottles were positive?

DR. MC ALLISTER: In these three instances, Dr. Salk?

DR. FRITZ: I can't tell you the number that were positive, Dr. Salk.

DR. SALK: All of them, or an occasional one?

DR. FRITZ: An occasional one.

DR. SALK: It would be a total of three bottles, or might it have been more than one bottle for each one of the three failures?

DR. FRITZ: I wouldn't say there were any more than three and probably more than one.

DR. SALK: Out of a total -- what is the denominator?

DR. FRITZ: Out of a total of 8.

DR. SMADEL: Do you use the same value, about 45 cc's per bottle?

DR. FRITZ: No, we use 5 cc's per bottle, plus a press.

it is a smaller bottle.

DR. [illegible]: What is the range of volume of these individual strained pools?

DR. SALK: 20 liter.

DR. FRITZ: They run from 15 to 20 liters.

DR. WORKMAN: I thought some were smaller sometimes.

DR. FRITZ: No.

DR. SHANNON: Have you any experience of late outgrowth in these things? I am thinking of Dr. Stimpert's.

DR. FRITZ: We have noticed this. When we went back and checked the bottles, the bottle showed no growth until it was passed on the 14 day tubes. Then it showed up in the final tubes. See, we go from bottles to tubes. I think that is the official method, and they show up in the tube but never in the bottles. There was just one bottle of the three.

DR. SALK: Show up in subculture only?

DR. FRITZ: In subculture.

DR. STIMPERT: Do you hold your bottles more than 14 days and observe them?

DR. FRITZ: No, we don't. We hold the pool to repeat them more than once if we have to.

DR. STIMPERT: But you don't hold the bottles from which you subculture?

DR. FRITZ: No.

DR. SEBRELL: Dr. McAllister, I don't believe you gave us your total monkey experience.

DR. MC ALLISTER: In the rocky, early start of which I suppose everyone is familiar, there were three monkey failures and since then there have been none.

DR. SEBRELL: No positive monkeys?

DR. MC ALLISTER: No.

DR. SEBRELL: And I believe you said you had never had a pooled lot fail?

DR. MC ALLISTER: In the early ones.

DR. SEBRELL: Within the dates you gave.

DR. SMADEL: Were the three positives in tissue culture tested in monkeys, or after they were reinactivated they were then put into a final pool and tested in monkeys?

DR. MC ALLISTER: After reinactivation they were retissue culture tested, then pooled, polyvalent tissue cultured, safety tested, and finally monkey.

DR. BODIAN: The three positive monkeys were also in bottles?

DR. MC ALLISTER: Yes, sir.

DR. BODIAN: And there were three in bottles that were negative?

DR. MC ALLISTER: This is our early experience. Yes, that is right.

DR. SALK: Dave, I think that some of those we found

positive in monkeys. You see here that the total experience between the two laboratories, I think, covered identical experience.

DR. BUDIAN: Either the bottle or in the monkey.

DR. SALK: Yes. We picked up some monkey positives that were monkey negative in their hands, but we always confirm the tissue culture positive.

DR. EDDY: I believe we got positive monkeys, but I don't think -- the most, as I recall, we didn't get over 2 out of 18.

DR. SEBRELL: We really shouldn't talk about the experience in the early days because I think the methods are different now.

DR. SALK: Dave was getting an idea of competence of the monkey. That is the only positive monkey experience.

DR. SEBRELL: Any questions?

DR. HULL: I would like to ask Dr. McAllister how long these samples were reheated.

DR. MC ALLISTER: Four days. When we reheated these three failures, that was three or four days?

DR. FRITZ: Three days.

DR. HULL: Three days at what temperature?

DR. FRITZ: 37.

DR. HULL: Was that after it was brought up to 37?

DR. FRITZ: Yes. 24 hours is allowed to bring it up.

I would like to comment Dr. Stimson's statement he made about the monkey tissue culture test. We have found in some tests experimental lots where you will get positive tissue culture in maybe a monkey. That has happened several times, so it appears the tissue test is much more sensitive than you have in a monkey.

DR. SEBRELL: I didn't recall, Dr. McAllister, your mentioning your experience with wild viruses.

DR. MC ALLISTER: We have none.

DR. SEBRELL: You have had no trouble with wild viruses?

DR. MC ALLISTER: None that we have been clever enough to detect.

DR. MC LEAN: I would like to stress a point that Dr. McAllister made. This is something that we have observed. In the material we made for the foundation the PH and temperatures remain constant in those. The material we made for the foundation, the field trial, and subsequent to that, we treated for nine days. We had a very low incidence of pickups, virus, in that. We did have some and we increased that standard period to 11 days to avoid this, and we were going along quite well up until the time we stopped sampling. Then we immediately, and a number of these are in that group, ran into a group of tests that were positive. We reviewed everything. You could almost draw a line on the

day, and the last was the day we stopped pulling the bottles out twice a day sampling them. In going back and reviewing the data we early in the game were pulling the bottles out of the incubator daily twice a day for the first three days for sampling, and thereafter to check PH, shaking them. We stopped the PH checking, but continued the bulk rate sampling and had to increase the time to 11 days. We stopped the bulk rate sampling and increased the time to 14, and then 16 and then 18 days. We were still getting positives. We went back to agitation in the incubator, which we now do routinely 40 hours, and we got no trouble at all. We dropped back to 11 days, and at the present time I think we have not had a positive strained pool in the last month. So apparently shaking is extremely important.

DR. SMADEL: How do you shake them?

DR. MC LEAN: By a shaking machine. We have a shaking machine.

DR. SMADEL: During the first 24 hours of incubation with formaldehyde.

DR. MC LEAN: Yes, sir, and experimentally we have tried adding formaldehyde prior to the final filtration step and that apparently gives a very good mixture.

DR. SEBRELL: Dr. Bodian.

DR. BODIAN: I wondered before we get away from the data that Dr. McLean and Dr. McAllister presented whether

Dr. Eddy could mention any results of regard tests that she has done on their lots.

DR. EDDY: Yes. In the spring I believe we got two monkeys -- I don't know whether I remember these exactly -- we got two monkeys on one lot. I know another lot I remember we got a positive monkey, but our tissue cultures were negative and I can't remember about the other one.

DR. CULBERTSON: That was last spring.

DR. BODIAN: There have been no positive monkeys since?

DR. EDDY: We tested, I know, some of our monkeys this year and we haven't had any.

DR. SEBRELL: I wonder if we could move along now to the next manufacturer, Dr. Barclay.

DR. BARCLAY: Dr. Hampil will speak for Sharp and Dohme.

DR. HAMPIL: We are so new at this game we don't have too much to contribute, I am afraid, except that as I have listened to people talking from the period of a year I have been associated with them and got into it, it has been very helpful in our particular situation, and I must say the limited time we have been operating we practically duplicated everything that everybody says. We started out testing rather heavily. Instead of making 30 liter strained pools, we are testing 12 bottles with one liter to make

bottles with 30 cc's of the material in the bottles. That means a total of 360 cc's from every 30 liter strained pool. That is after we finish the activation, of course, and we are running into some cases that everything comes through clear throughout. In cases we may have 7 out of 12 bottles that show virus and sometimes it is only 1 out of 12. In every case up to the present time that we have had time to complete they have typed out as true. If it were a strained one we were inactivating it would be a strained one that we would pull out of the bottle.

Now we are not getting degeneration of the bottles except in maybe only one case, but in the majority of cases degeneration of the bottles does not occur until after the seventh day change. It will occur about the third or fourth day, and then when it goes it goes very fast. We do have some bottles where we have had the bottles negative right straight through and then subpassage B tubes would go. We are not holding our bottles just the 14 days, and we can get the same picture within the same series. We can get one bottle going after the first change. We could have another bottle in that same series where you don't pick up anything until we get to subpassage B.

We have had experience of having a nine day incubation Where we are getting into some trouble we decided to increase our time from 9 to 12 days. We have had at least one experience

where strained pool was negative at 3 days and it was positive at 12 days and it turned out true. So whether we put things in when we are doing our work, it is hard to say.

DR. SEBRELL: What is your agitation?

DR. HAMPIL: Oh, we have done several things trying to prove, Dr. Sebrell. At first we were agitating just by hand by shaking and shaking maybe every hour or two hours. Then we went over to making our strained pools, adding the formin slowly, getting a good mixture and drawing that over into another bottle to give a really good mixture there, putting that into a water bath then to be sure the temperature comes up, then into the incubator. Then, of course, the shaking we would get during the first three days would be when we were taking our samples. Then we are going back and shaking the bottles three or four times a day. But we are not using a shaking machine as was described by Dr. McAllister.

DR. SEBRELL: How about your inactivation curves?

DR. HAMPIL: Oh, they are not straight lines. We get nice straight inactivation lines when we just do something experimentally with about 100 cc's or 150 cc's of material. But in our bulk they are not straight.

DR. SEBRELL: How about your wild virus experience?

DR. HAMPIL: We haven't had any so far.

DR. SEBRELL: How about your total monkey experience?

DR. [illegible]: We have only two lots that have come through the monkeys. The first lot passed all the tissue culture safety tests. We were trying to accelerate our program in order to get some material out. Therefore, we were putting materials into the monkey on lot two and our third mixture before we had the tissue culture safety test off. Those two lots of monkeys came through quite satisfactorily although the tissue culture safety test was positive.

DR. FRANCIS: I think, Dr. Sebrell, this brings up again the point that most of these monkey tests aren't being done at the same time. Consequently, they are not really comparable.

DR. SMADEL: How many tissue cultures were positive and how many monkeys were positive on comparable material?

DR. HAMPIL: Well, we haven't gone far enough to know just what our real experience would be. We have only made three mixtures. We have made more than that -- there is some in monkeys now -- but we have three mixtures, two of which had virus in the tissue culture according to our tests and typed out, and they didn't show anything in the monkeys. Now fortunately or unfortunately, we have another lot on in the same category right now.

DR. BODIAN: What I think Dr. Smadel wanted to know was the ratio of positive bottles in those two lots. Was it just one bottle down or seven bottles down?

DR. HAMPIL: It was 19 bottles down.

DR. SABIN: 19 out of 19, and monkeys negative?

DR. HAMPIL: Yes.

DR. SHANNON: In the individual strained pools that went into those mixtures they proved out negative. I would gather otherwise they would not have been mixed.

DR. HAMPIL: Well, of course, you are embarrassing me again. I was trying to accelerate the program, so that we actually put our strained pool tissue culture test on at the same time we put on our vaccine.

DR. SHANNON: Then this does not represent a pick up at a later date having passed earlier?

DR. HAMPIL: No, we can't do that any more, of course, but that was an attempt to do some acceleration.

DR. SEBRELL: Dr. Fritz.

DR. FRITZ: Betty, do you make a transfer during the course of your inactivation to a sterile bottle?

DR. HAMPIL: Only the first time after we add the formalin.

DR. FRITZ: Not during the inactivation period.

DR. SEBRELL: I believe Dr. McAllister said they change theirs.

DR. FRITZ: We do, too.

DR. SEBRELL: You change during the inactivation period?

DR. FRITZ: Yes.

DR. [illegible]. Do that on questions of Dr. Kempel, now? I would like to try to move around and get around to the manufacturers before we break up for lunch so we don't have to hold them unnecessarily long if we can do so. Now, Dr. Bozeman, are you speaking for Pitman-Moore?

DR. BOZEMAN. Yes, sir, in a general sense, and then for specific questions we will call on Dr. Bruckner. Now there is one thing I might point out first which may or may not be important. That is that we do not prepare the tripsan as product. Our product is prepared according to the Kenalt procedure, and there has been no change in the methodology to my knowledge since we first started. We inactivate in roughly 40 liter qualities in stainless steel. Those are brought up to a temperature under conditions of vigorous agitation in a water bath in about 20 minutes. We plot a 4 point inactivation curve. Then we use the factor of three times plus one day. We added an extra day about one year ago at the time that some of the other firms were having difficulty.

At this time we have completed the testing on approximately 40 lots. We have had no positive tissue cultures in either tubes or bottles, but we have had one positive monkey. This slide was sent to Dr. Bodian earlier this year. It is my understanding that the lesion was very minimal. We observed no symptoms whatsoever in the monkey and Dr. Bodian expressed

the opinion that the lesion was so small it probably would not have caused symptoms in the monkey.

We hold it routinely for the 14 day period. However, on occasion they have been held 21 days with no change.

DR. SHANNON: Did you resection that one positive monkey?

DR. BOZEMAN: Yes, it was resectioned. Perhaps Dr. Bodian has the report on that monkey. I didn't bring it along.

DR. BODIAN: I have my letter on this. I was hoping for a chance to comment on monkey versus tissue culture altogether at the end.

DR. SEBRELL: Maybe we can do that this afternoon.

DR. BODIAN: Do you want to hear what this monkey showed in particular?

DR. SEBRELL: Let's save that until this afternoon, Dr. Bodian, if you don't mind. How about your wild viruses?

DR. BOZEMAN: At this point we may have for the first time a wild virus. We are not certain. Up until this point or previous to this we have not had wild viruses. We have had some called nonspecific degeneration on one test involving strained pools from roughly eight lots. Now this factor was not transferable. These lots are all on retest at the present time. Those tests will be completed this coming Wednesday and as of this date they are clear.

DR. SMADEL: Are do you [illegible] them?

DR. BOZEMAN: We agitate while we are heating to 37. The agitation is very vigorous, a propeller inside the tank, two bladed propeller set at different heights within the column of liquid. Then at 48 hours we transfer from the sealed agitation tank to a different type of storage tank and tear right on at 37. The transfer that is made at 48 hours there is no agitation during the inactivation period.

DR. SMADEL: But during the first 24 hours the agitation is only during the time when the batch is coming up to 37 degrees.

DR. BOZEMAN: Right. It takes only 20 minutes, Dr. Smadel, for us to heat up to 37.

DR. FRANCIS: But you still continue it for 24 hours?

DR. BOZEMAN: Not the agitation, no.

DR. SALK: When you speak of wild viruses, at what point do you observe them?

DR. BOZEMAN: We have had none, Dr. Salk.

DR. SALK: Well, I think it is important at some point to understand whether this is after inactivation has been completed or is it in the raw fluids before inactivation or is it in the cells used for tissue culture for safety testing. This is just a general question.

DR. BRUCKNER: This particular case was on material which -- it is going on right now -- actually was in the case

of material which had been through the inactivation period, and the first note that we saw of what looked like some kind of specific degeneration was between the 3rd and the 7th day. Now those were just transferred to their first subculture yesterday, so whether transfer or not, we don't know.

DR. SALK: Was this observed in the uninoculated subcultures at the same time?

DR. BRUCKNER: No, and the reason I am quite sure it is some kind of agent is there was only part of 8 or 10 different pools in the serial lot of one set of tests that showed this degeneration. One pool showed it and that pool is a part of that serial lot. We have controls in addition to our uninnoculated controls. All the other lots in bottles are also all right, and it could hardly be coincidence that one pool in that serial would show some degeneration.

DR. ENDERS: How much is your innoculum in the bottle per bottle? How much do you innoculate in the bottle?

DR. BRUCKNER: We are using only small bottles now and doing 5 cc's to about 10 cc's.

DR. SHANNON: Could you tell us with your regular routine experience where you attempt to draw an inactivation curve; assess the time and add one day, you would have 120 minimum of those individual strained pools. Now what has been your experience at that stage?

DR. BOZEMAN: We have not had a single positive tissue

culture.

DR. MC LEAN: Even on the strained?

DR. BOZEMAN: Even on the strained pools.

DR. SALK: On what volume?

DR. BOZEMAN: Roughly 40 liter. They will vary a little. Some may run close to 50 and some may run, let's say, down to 33, but they are roughly 40 liters.

DR. BODIAN: And what is the minimal inactivation time? Do you have some sort of a notion?

DR. BRUCKNER: I meant to add to what Dr. Bozeman said that we do not actually draw a line in trying to find out the place where the line would cross the zero base. What we are doing is running these four samples to detect any changes or anything out of the ordinary, and at 72 hours we have never found a virus in titer greater than ten zero. In other words, never more than five tubes diluted out of 10. No virus at 72 hours. So it is between 48 and 72 that we get either to zero or to no detectible virus.

DR. SALK: And your standard procedure is ten days?

DR. BRUCKNER: And we carry it for ten days.

DR. ENDERS: I would wonder if the people here would be -- I think this agitation is quite evidently a crucial point and I don't know why we haven't thought of it before because we do know that oxidation, a lot of oxygen tends to inactivate some viruses very rapidly, and since your experience

has been so good I would like to know whether the other manufacturers here feel that their agitation has been more active than theirs in comparison between the two, the degree of agitation that you have all used, in other words, so we could get some idea what is the best procedure.

DR. BOZEMAN: Perhaps I might tie it down for them, Dr. Enders, if it would help. We actually use for inactivation and for our heating to 37 the vessel recommended by the Agricultural Research Service for the pasteurization of the serum, the same agitators, the same set up, identical, and if you have worked with that you know that it is very vigorous.

DR. STIMPERT: That is only for 20 minutes?

DR. BOZEMAN: That is only for 20 minutes.

DR. STIMPERT: Then you do not agitate after that period?

DR. BOZEMAN: At 48 hours we make a transfer from this vessel to another vessel of the same type, the only difference being that the second vessel does not have an agitator.

DR. STIMPERT: And you don't shake or agitate?

DR. BOZEMAN: No.

DR. STIMPERT: And this agitation is at the time that you add the formaldehyde?

DR. BOZEMAN: Yes.

DR. STIMPERT: You add the formaldehyde before or

or during the agitation?

DR. BROWER: Before, immediately before. That is the last step before.

DR. SMADEL: Mr. Chairman, I would like to return to a question that Dr. Salk raised. Perhaps I didn't understand the answer. Maybe I would like a more general answer from the various groups. Has anyone any evidence that a wild virus has been found in an inactivated lot of polio vaccine that presumably came from the formalinized lot of vaccine and not from the cells that were used for the safety tests?

DR. WARD: I think, Dr. Smadel -- now I cannot give you a definite answer and I apologize for not having come with some data, but there were other things happening. I am still a little bit sensitive about your calling me a reluctant patient. I want to assure you that I am not. I think that we saw one lot like that, but of course, even running controls -- and I would like to have as soon as I get through Dr. Hoolihan speak of our experience with wild viruses -- that you end up at a point where on controls it doesn't show in every tube, and since you cannot run as many controls as you have on the other side that you end up on the horns of a dilemma as to where this thing came from.

DR. FRANCIS: May I ask a question?

DR. SEBRELL: Yes, Dr. Francis, but we still have Dr. Dettwiler here to give us their experience.

DR. FRANCIS: I wanted to ask Dr. Hampil and Dr. Bozeman about their bottling and filling. Is that done in a separate area special area?

DR. BOZEMAN: Yes. Our production is in an area isolated from testing, and then testing is separate from filling. Actually our material is handled in five separate units with no connection point.

DR. HAMPIL: All the tissue culture safety testing is done over in the research building and the rest of it is in production.

DR. SEBRELL: Dr. Dettwiler, would you give us your experience?

DR. DETTWILER: I would like to review just by way of comparison what our experience was last spring, winter and spring with the clinical material. At that time we were handling 40 liter single strained pools in single glass container and the agitation at that time consisted of passing the virus solution through a coil to raise the temperature to the incubator temperature, during which, or right at the same time formin was added. So we were getting good mixture of the formin and also getting the temperature up rather rapidly. The material then was transferred from the original bottle to a completely new bottle, and that was the extent of the agitation, the formal agitation at that time. Sampling, of course, was done for the inactivation curve, but

I believe most of you can imagine that a 20 liter glass container can't be agitated very much even to get a sample.

Our experience with respect to safety test last year -- Dr. Culbertson and Dr. Hull can correct me if I have some of the information incorrect -- we had evidence in monkeys from the first two lots and the last lot we processed. I think it is fair to say that the first lot represented some variation from the subsequent lots, but the last lot as far as we could tell was processed as nearly as possible to the ones ahead of it. In only one of those did we have a positive tissue culture result, and that not in the usual or the recommended tube test. Isn't that right, Dr. Hull?

DR. HULL: That's right.

DR. DETTWILER: But it was in a bottle.

DR. SALK: One of the first two lots?

DR. DETTWILER: Yes, I believe we had one monkey on one of those lots, one monkey on the other lot, and one monkey on the other lot. Can you bring me up to date on what we did over and above the tube test last spring?

DR. HULL: On most lots we tested 150 milliliters in bottles in addition to the 40 roller tubes which were recommended. With that addition we were testing as much per lot as we are now required to by the minimal requirement. In other words, one milliliter per liter.

DR. DETTWILER: But at that time that represented a

test on the trivalent or the material which is built on that we are doing now in volume.

DR. HULL: That's right.

DR. SHANNON: On that have the strained pools been tested?

DR. DETTWILER: Last year, no. It was only tested in the final trivalent mixture.

DR. SHANNON: You had one positive bottle, no positives in the ordinary roller tubes?

DR. DETTWILER: That's right.

DR. SHANNON: What was the volume again?

DR. DETTWILER: 40 liters in the strained pool.

DR. SHANNON: No, I mean in the test.

DR. HULL: We carried 150 milliliters in three bottles plus the 20 milliliters that went in the 40 roller tubes that was recommended.

DR. SHANNON: And you had one positive bottle?

DR. HULL: One of three bottles was positive. We carried 50.

DR. SHANNON: As I recall, that was the first time a positive one had been turned up in bottles.

DR. DETTWILER: I think so. Our experience starting last fall -- as you can imagine, we change our methods to take care of increased quantities. Our first few batches were done in glass, but by far the majority of the production has

been processed in stainless steel tanks with each of the monavalent strained pools having a volume of approximately 400 liters, plus or minus the monoliters.

Our typical procedure or our standard procedure is one in which the filtered virus solution is added to a 400 liter tank. It is then pumped through a heat exchanger to bring the temperature up to 36 degrees Centigrade. This takes a period of approximately two hours to bring the temperature to that point. At the end of the circulation, or let's put it this way -- when a temperature is up to where we want it, 36 degrees Centigrade, and while it is still in circulation the formalin solution is added. Now these tanks are so designed that while there is foment of liquid, we have attempted to minimize foaming. There isn't much splashing to speak of and there is agitation, but I am sure it is not as vigorous as Dr. Bozeman described. When the formalin is all in, that tank, the contents of that tank are completely transferred to a new tank which takes 20 to 30 minutes.

Now that is the extent of the agitation in our process. Again it is very difficult to agitate a tank of that size. You can twist it and turn it a bit, but I am sure you don't accomplish very much. The processing then insofar as agitation is concerned, we perhaps should mention that whenever we are through with an inactivation of a monavalent strained pool it is transferred by a similar pumping

arrangement of vacuum or pressure, so the vaccine has been in either 200 liter tanks or possibly 5 gallon pyrex bottles. This, of course, is when formalin is still active, has not yet been neutralized, and the temperature would be fairly warm.

Our inactivation experience is something like this We do establish a curve, taking samples, I think, at about 16, 32, 48 and 72 hours. We do establish a time. We use the factor of three as we did last spring, and our first few trials last fall were on that basis. We had some positive tissue culture results. We then arbitrarily added 72 hours to our incubation period. So that the practice with the majority of our lots has been the indicated time with the factor of three.

DR. SHANNON: What would the indicated time be, about?

DR. DETTWILER: Around 9 days, 8 and a half to 9 days. So that the indicated time plus three days, or 72 hours, would be in the neighborhood of 11 or 12 days in the majority of the lots. So it would be a little shorter but not very much, fairly uniform.

Now our experience with tissue culture safety -- before I go on to that, our tissue culture safety testing is done in a 16 ounce prescription bottle with 27 cc's of vaccine and 54 cc's of medium.

DR. SMADEL: How many cc's of vaccine?

DR. DETTWILER: Yes. The [illegible] sequence that is recommended in the minimum requirements is followed. The bottles are not kept after the 14th day, although pooled material from each bottle is maintained in case we have to go back.

DR. SMADEL: How many bottles in all?

DR. DETTWILER: In the Monavelent we will usually put on at least 20 bottles. We don't need that many, but the losses by contamination and otherwise, we try to put on this sufficient margin to end up with the required amount.

The same sequence or procedure, of course, is followed with the trivalent pools. At this time another sample or a portion of the same sample is injected into monkeys for the monkey safety test. Now our experience has been rather varied. We were embarrassed by having gained perhaps too much confidence from our experience last spring. We put monavalent strained pools on safety tests, mixed the lot immediately, and had the trivalent safety test runnin at the same time. We found a lot of virus in some of them. We have had positive tissue culture safety tests on trivalents in which the monavalents have been clean, and we have had monavalent tests which have been satisfactory -- I guess that is what I said, but we have had trivalents clean when the monavalents were positive, and that sort of set-up. We have had some monkey positives. In each instance, I think

I am correct that we have had positive tissue culture result maybe we have had a monkey positive.

DR. SHANNON: You have never had a positive monkey without a positive tissue culture?

DR. CULBERTSON: Not this year. We did last year. We have only had one positive monkey.

DR. FRANCIS: And how many positive tissue cultures?

DR. DETTWILER: Eight monavalent, of which five of those are incriminated with the trivalent pool, and we have had 7 trivalent mixtures, but one of those has been positive the second time after the reincubation.

DR. FRANCIS: And out of these total of 8 instances where you had the monavalent tissue culture positive, or 7 trivalent positive mixture, you have had only one positive monkey?

DR. DETTWILER: That's right.

DR. SMADEL: You only test the trivalent with monkeys?

DR. DETTWILER: No.

DR. SMADEL: Both monavalent and trivalent?

DR. DETTWILER: Yes, tissue culture.

DR. SMADEL: I mean in monkeys.

DR. DETTWILER: Just the tissue test.

DR. SEBRELL: Any further questions? Did you finish?

DR. DETTWILER: We have had a lot of experience with wild viruses, and I would like Dr. Hull to give us that

that information.

DR. SHANNON: Before you go on to that I would like to ask the question we have asked other people. In retrospect when you have had a positive culture and attempted to find out, as I am sure you did, from the processing data, has there been any clue to something that had gone wrong that had it been called to your attention at the time you would have been suspicious? I am talking now about inactivation curves, rate of inactivation, a curved line as opposed to a straight line, anything of that general sort.

DR. DETTWILER: Nothing of that sort. As I mentioned earlier, the majority of the lots have been processed with an additional 72 hours over and above the indicated time, so we felt that what slight variations you might see in the curve would have been taken care of by the additional 72 hours over and above the calculated times.

DR. SHANNON: And your process actually gives you about four times the calculation?

DR. DETTWILER: That's right, and more recently we have extended that. Now currently we are extending the inactivation time for type 1 an additional 48 hours, and for type 2 and 3 for an additional 72 to 96 hours.

DR. SHANNON: Over and above the 72?

DR. DETTWILER: That's right.

DR. FRANCIS: When you had these breaks would these

likely to one type rather than another?

DR. DETTWILER: I think the majority, type 3 was found most often. Isn't that right?

DR. HULL: Type 3, I think, was found 11 of 17 times, and I feel fairly certain that it will be 12 and 18 by the time we go back.

DR. DETTWILER: There will be 12, yes. But Dr. McLean's information explains perhaps why that happened. If we had looked longer perhaps--

DR. SEBRELL: Are you going on about the wild virus experience, Dr. Hull?

DR. HULL: Yes. I would like to say one more thing about the polio, if I may, first. I think that in safety testing for polio virus that perhaps we have two things to consider, one being that we are testing for one of three laboratory strains of virus which we are familiar with and which we know how it will act under certain circumstances. Now we know, for example, that if we take any of these three viruses, dilute them out to where we have one infective dose, we can put that into a bottle and within 7 or 8 days there will be no damage in the bottle, but any half million liter that you take out will have live virus in it. By 14 days the bottle will be destroyed, all of the subcultures will have virus, and the titers will be out beyond 10 to minus 6, 7, out in that area. So that if we are only checking for these

three strains of viruses unaltered I think that our present safety test is quite adequate. Some of the other things which Dr. McLain has mentioned, and others and which we are beginning to see also, may be the results of things we don't know about, and I think we might consider those two points in whether or not the safety test is adequate. I personally feel it is adequate for detecting the smallest amount of these viruses of which our tissue cultures will pick up. We have just recently come across cases where at 14 days we had no damage in the bottle, but we had one of four subcultures positive or perhaps 2 of 4 subcultures positive. In one particular case we had one bottle positive at 7 days, all subcultures positive. That same bottle was positive again at 14 days. But on the same lot one additional bottle had three of four subcultures positive and another bottle had one of four positive. Until we saw this I would have been willing to have said that any time that one infective dose was introduced with the vaccine that by 14 days we should have it and should be seen immediately.

Now if these cases are true, and the even more extreme cases which Dr. McLean has mentioned, if those are true then do we have an altered virus? Do we have another virus introduced from outisde, and if so, do we have to devise our tests to detect those things.

As far as the wild viruses are concerned--

DR. SALK: [illegible] the denominator for the "positives" you mentioned, Dr. Dettwiler, the number of instances where you have picked up infectious virus, but what was the denominator for that total experience?

DR. DETTWILER: Well, with the trivalents it is about a fourth of the total.

DR. SALK: How many?

DR. DETTWILER: One fourth.

DR. SALK: One fourth of the total. In other words, 7 out of 28. And the monavalent?

DR. DETTWILER: Well, some of those no doubt were duplicate.

DR. SALK: You had 8 monavalents.

DR. DETTWILER: It would be three times that many monavalents.

DR. SALK: 28, would be a hundred and--

DR. SHANNON: 81. Three times 28.

DR. SALK: Three times 28.

DR. DETTWILER: That's right. In other words, if we hadn't been doing those things concurrently--

DR. FRANCIS: You mean if you just hadn't made your pools before you had your first test it probably wouldn't have happened?

DR. DETTWILER: That's right, in all except a few

instances.

DR. SHANNON: That is about the same percentage as Fred reported, 8 out of 81.

DR. SEBRELL: Dr. Hull, do you want to go ahead?

DR. HULL: In regard to these wild viruses we seem to have had more than our share of them, and what I can gather talking with the other representatives, I think that at present we have possibly 7 or 8 agents. One of these which we call wild virus 2 has re-occurred several times, and another we are referring to as wild virus 4, I don't have the count on. In the last month it has just hopped up everywhere. I think we had one shipment of monkeys probably that must have been loaded with this particular virus, and it has caused us a great deal of trouble. One of them which I refer to as wild virus 1, was isolated during the field trial and is in some way tied up with the ARD or APC group of viruses. It differs only in that it will not grow in heli-cultures. It crosses over on CF test, and we have found a large number -- not a large number -- we have found a fairly high percentage of human sero-tests that had CF antibody to it and a few neutralizing antibodies.

One point that I think Dr. Salk brought up regarding whether or not these viruses have been found in the inactivated vaccine, that, of course, is the one thing we

all would like to know, and I am sorry we do not have definite evidence to say yes or no. We have one case which is under test now in which I think we have evidence that this is not true. In the monavalent test on one type we had 17 of 20 bottles with this wild virus 4 in it. The bottles were not destroyed. The subcultures were, but when we went back to those bottles again, to samples that were saved in the refrigerator, we again subcultured the same virus out. So we felt it did come from the bottles, not the roller tubes themselves. In one of the monavalents I said we had 17 from 20. Another one we had 15 out of 20, and another one we had 13 out of 20. Now the same monavalents have been pooled into trivalents which have been tested twice, and none of the trivalent material shows it.

DR. SALK: What about the control cultures at the time you detected what you thought came from the monavalent pool?

DR. HULL: In some cases we have seen that and some we haven't. The number, I think we have seen it like maybe one out of five controlled bottles. Out of a 20 bottle test we would usually carry 5 controlled bottles, maybe sometimes only 3. So that your percentage of controls in comparison with percentage of tests sometimes will eliminate finding these things in control.

Now we have started inactivation tests, and unfortunately the only one completed at this time is wild virus 2, which

was our most frequent isolate until recently, and wild virus 2 is knocked out by formaldehyde before polio. Most of them are filterable and two of them, I believe wild virus 2 and one we call wild virus 6, are fairly heat resistant. They will withstand 65 degrees for a half hour.

One more point and then I will give the floor. We have on one or two occasions, one that is outstanding in my mind, almost missed polio because it was tied in with one of these wild viruses. It was just caught on the tail end going through, in which there was occasionally one bottle out of 20 that had polio virus in it and it was almost missed because it was masked by one of these wild viruses. But fortunately by the use of different antiserum this was detected and that lot reheated.

I think that is about what we have.

DR. CULBERTSON: We put some of these wild viruses in monkeys. I think maybe you ought to mention it.

DR. HULL: We have planned to put them all into monkeys. At present we have put wild viruses 1, 2 and 4 into monkeys, and in various routes, intracerebrally, intraveniously, intramuscularly, and into the trachea, and so far we have not been able to produce any disease at all, nor temperature rise, in some cases not even antibody. However, most of them do produce good antibody in monkeys or rabbits.

DR. [illegible]: Of course, we had no antibodies to begin with.

DR. HULL: That's right.

DR. SEBRELL: Dr. Dettwiler, I don't believe you mentioned separation in your plant of various parts or processes. Do you carry some of it in one building, some of it in another?

DR. DETTWILER: Earlier the separation wasn't as good as it should have been. We have since corrected that. I think we must admit that we had doubts in our mind about the possibilities of contamination of samples and things like that. But, as you can imagine, those things are very difficult to prove.

DR. CULBERTSON: I don't think our measures thus far have lessened the wild viruses at all so far as I know.

DR. SEBRELL: Well, we have Dr. Ward. Dr. Ward, would you tell us your experience?

DR. WARD: As I have already indicated, I don't have, unfortunately, figures on data here. I would like to say going along that we have followed some of the practices here with respect to inactivation. We have added formalin, transferred the single strained pools over to the other containers, and those have received some shaking, but not actual mechanical agitation. We earlier, I think, due to Mr. Houlihan's experience, last year, did follow the curve on

inactivation, and when it became quite apparent that we ended up with this same spot, problems that others have now explained, so I won't just repeat that. In other words when we followed the curve and multiplied by a factor some of them went through beautifully and some of them gave us a problem. We have seen, and here again I do not have data, instances where single strained pools passed and the polyvalents after mixing would fail on tissue culture safety.

DR. FRANCIS: You did not have that experience?

DR. WARD: We have received that experience, yes. With reference to a differentiation as to whether we have had positive monkeys and negative tissue cultures, I cannot recall. We have been working until very recently with unpreserved material which we felt because of possible contamination problems and refiltration would cause potency problems. So we have followed the practice of making a polyvalent pool, immediately going to tissue culture safety and to monkeys, and I cannot remember in my own mind any breakdown of the relationship between those. I would say that our own personal impression is that the tissue culture safety is a more sensitive tool than the monkey.

We have seen some diagnostic problems on intracerebral monkey safety test where they were apparently -- Dr. Bodian has seen one or two of those -- new types of lesions which apparently got into the picture. In other words, the only

thing I am trying to indicate, that apparently the interpretation of the monkey safety test can still be somewhat of a problem pathologically, which brings, of course, always some doubt in my mind that -- believe me, Dr. Bodian, I am not questioning you. I can appreciate the position you are in. At times I am sure that some one must feel as though they are sitting on a very narrow ledge.

With respect to quarters and so on, we early worried about that. After Dr. Houlihan's work of last year I think we were somewhat misled because his early experience was extremely smooth. In retrospect it was too smooth. We have had our quarters somewhat together. We have tried to space working, though, within those quarters so that everything wasn't happening at one time and to keep them extremely clean.

As I have already indicated, we have had what we feel is too much of a wild virus problem, and the discussion of that I would like to turn over to Dr. Houlihan.

DR. SEBRELL: Dr. Ward, can you recall your total monkey experience?

DR. WARD: No, I can't. I am sorry.

DR. SHANNON: Could you tell us something about the size pool?

DR. WARD: We have been running single strain pools from 30 to 50 liters, and hence the polyvalents are somewhere

between 90 and 150 liters.

DR. SHANNON: Do you recall on some of your batches where you did get positive tissue culture and then again returned to the original innoculation data, was there anything peculiar about them?

DR. WARD: No.

DR. SHANNON: What is your inactivation practice now?

DR. WARD: Well, we start off -- and you check me on this, Ralph -- in the neighborhood of 8 to 9 days. We had some show positive and some came along rather well. We then studied the curve using bottles, and we moved on out fairly rapidly and we got the impression that as we moved on out, and at the same time we were always drawing some points on the curve in a method similar to what Dr. McLean has mentioned, so that we have gone out, well, quite some time back to around a 14 day standard. When the minimum requirement came out, the potency line was drawn. I wondered some about that. I still sincerely feel, even before coming here, and after listening to this, that there seem to be some problems. We have our own problems. We make impirical moves. We will get a fair or good experience for a time and then we get sort of bitten again. We are either awfully unintelligent or there are a number of things here which seem to jump around. It is one of the most difficult things that I personally have ever tackled, and I have felt until now that I have been in

on some pretty complicated ones.

DR. SHANNON: Could you give us a general estimate of your experience on the safety tests with the single strained pool? Fred has been getting about 10 percent contaminated.

DR. WARD: I am sorry, I just can't do that. The data is there.

DR. SHANNON: Could you let us have it later?

DR. WARD: I imagine probably Dr. Workman's men are there and if they are there when I get back -- they are going through everything at the present time.

DR. SHANNON: What size innoculant do you use for safety test?

DR. HOULIHAN: In the single strained pool we use 10 cc's of vaccine, 20 cc's of medium. We use approximately 6 or 7 of those, so we are overtesting according to requirements. In our polyvalent pools we use 25 cc's of vaccine and 50 cc's of medium, and those are tested in flake bottles, and we use enough of those to fill the requirements of the one cc for a liter of vaccine.

DR. WARD: I might just remark with reference to the situation, and this was -- as I say, we see these problems off and on, and before actually I heard of any of these problems we had set forward in motion a program to double the tissue culture safety test volume experimentally to see what we would get into. In other words, I was just

curious to see if then we started picking up thing. I don't think we have seen anything to indicate Dr. McLean's experience, but I am not sure that we have carried on the tail end of things what we have seen as the live virus problem.

Now I think Dr. Hull's comment is quite appropriate, that maybe we have possibly missed something there by this masking business because of the live virus problem. It started biting us, it seemed, quite early and we wrestled around and I am worried about it. I called Dr. Workman and we actually sent some samples in to Dr. Habel, and one, I think, to Dr. Eddy, an my whole -- without any basis the thing was if we saw these things were there some we couldn't see that possibly might not be cytopathogenic, and which way do we go. Now maybe that is an unnecessary worry. I just don't know. I would like to have Dr. Houlihan comment on the wild virus.

DR. HOULIHAN: On that last comment about the possibility of non-cytopathogenic agent, we actually manufactur- commercially such a vaccine. It is grown in tissue culture and the agent produces no psychology whatsoever. So we have evidence then of a virulent virus which grows in cells repeatedly, actually don't have to add more virus, just changes cells. We have picked up approximately 7 strains from tissue culture safety tests. We haven't identified all of it serologically, Dr. Hull, but we find two of them are related to Safin's HE strain. We have also picked up two

strains from feces of normal monkeys, four strains from feces. We have studied the inactivation by formaldehyde of four different strains, and all of these were inactivated in less than 24 hours. We have tested those same four in monkeys intracerebrally, observed them for 26 days, and ran the routine pathology, and those are all negative.

DR. FRANCIS: You innoculated in the monkey test intracerebrally?

DR. HOULIHAN: Yes.

DR. STIMPERT: Seven strains?

DR. HOULIHAN: Four which we thought were different. We are studying morphologically. The majority of those are neutralized by normal monkey serum.

DR. HULL: Some time ago we quit using monkey serum for typing. At one time we called one of these wild viruses polio because it turned out, I think it was our type 3 monkey serum had an antibody against this particular agent.

DR. WARD: I think we have got that type of experience, too. Back in some of the phases of this thing it looks as though we were getting polio and it is wild viruses because of monkey serum.

DR. HOULIHAN: We tried to isolate these from the monavalent pools to repeatedly prove whether they were present or not, and on those occasions I can't remember how many times we weren't able to isolate it; in view of the fact

that the first four or five we had isolated were so susceptible to formaldehyde we thought perhaps they were being taken care of on inactivation.

DR. SEBRELL: Well, gentlemen, it is getting on to 1:25. The blood sugar should be getting low again. I think we better take a little break for lunch. We have been around the manufacturers. They are all invited to have lunch with us. We will all lunch in the clinical center. I think this afternoon we had better have a meeting of the Advisory Committee without the manufacturers present, and so before we adjourn for lunch I would like to give Dr. Ward an opportunity to add anything he would like to add, or the representatives of the other manufacturers to say anything they would like to say to the Committee, and then we will adjourn for lunch. Dr. Ward, is there anything you would like to say?

DR. WARD: I don't think that I have any worthwhile comments to add that would be helpful. Ralph, do you have any?

DR. HOULIHAN: No.

DR. WARD: I think from everything I see, it has been pretty well covered here, and unless you gentlemen want to ask me anything outside this group, why, I just want these gentlemen to know that I have said everything in front of them because our relationship has been very good.

DR. [illegible]: Just for clarification, how often do you find the wild strains in the trivalent?

DR. HOULIHAN: I don't recall. I would guess probably two occasions. The majority of them have been in the monavalent.

DR. SEBRELL: Are there any other questions anyone would like to ask? Dr. Bodian.

DR. BODIAN: I would like to ask whether in the bottle test any serum is used at all in the medium in any of these laboratories.

DR. STIMPERT: Yes, calf serum and--

DR. BODIAN: So it has no inhibitor to polio virus. I wonder what the general experience is.

DR. MC LEAN: It usually does not.

DR. BODIAN: I think that is rather important because there are sera which would inhibit polio virus, the calf serum being one in our experience which did not. We have had experience with horse serum, ox serum, which did inhibit. So in the bottle test I think it would be interesting to know whether those are used.

DR. BOZEMAN: We do not use serum at all in our test. I have been quite interested over the past year in processing differences that have necessarily occurred, because some of us were tripsinizing and some of us were not, and if I have understood properly, we have not been able to use the same

filtration methods for example. I think it might be interesting to know whether or not there is a real difference between these two products. Now Lilly and ourselves, if I understand correctly, do not tripsis. Otherwise we use identical methodology except for volumes handled. Our volumes are considerably smaller than those handled by Lilly at one time. Also I would like to know whether or not Dr. Workman has found major differences in the potency of this material by firms, if there is a possible correlation of that type.

Now it has been my impression that against the type 1 control serum we have not done well. On the other hand, we have had no apparent problems with safety and perhaps the correlation of those two points may possibly shed some light.

DR. BODIAN: What about serum and other--

DR. HOULIHAN: We start our serum off with two percent horse serum. At the end of seven days we move--

DR. BODIAN: This is before innoculation?

DR. HOULIHAN: Yes.

DR. SHANNON: Are there any other comments?

DR. STIMPERT: I was going to ask when we are dismissed are we free to go home?

DR. SHANNON: Yes. I think you have given the Committee an awful lot of factual information. It will be helpful to them. I realize, too, that for the first time each of you has been exposed to some of the problems of each

of the owners. We would appreciate it if you would think over very seriously what you have heard, talk it over with your technicians, and in the next day or two when you are back in your laboratories write us a note, either Dr. Sabin or Dr. Workman, emphasizing perhaps the important points that you feel should be stressed having to do with inactivation, having to do with safety, having to do with the relationship of tissue culture versus monkeys, anything that you feel should be given further serious consideration.

Now the reason why we would like this serious consideration given is with the factual data available to us on problems having to do, or on processes having to do with inactivation times and the like, for instance, processes having to do with safety procedures and the like, it has been impossible for the Committee to make a clearcut separation or to make any positive separation between those lots of vaccines that are potentially suspect and the other lots in the Cutter process, or to make cleancut separation between the lots as we have seen them from Cutter and the lots that we have seen from the other commercial houses.

Now there are differences in processes, there are different points that are born down by each of the different manufacturing groups, but we can't escape the conviction that with the information we have this could happen in another laboratory some time in thefuture; and I would say that as

far as the Committee is concerned, it has not completed digging in to the extent it is possible to dig into problems that could have precipitated this difficulty if it is an actual infection of individuals with live vaccine, but that they are concerned about the generality of the problem as much as they are the specific problem facing Cutter at the present time.

Now we do hope that if these thoughts occur to you they be frank letters to the Committee or to Dr. Workman. They will be considered in the nature of privileged communications, and we would appreciate your help. Yes, sir?

DR. CULBERTSON: Dr. Hull didn't answer Dr. Bodian's question for us about the serum.

DR. HULL: We start the cultures with two percent horse serum, and at the time that they are used that is withdrawn and the culture is rinsed three times with medium 199. We have tested those as compared to cultures without serum and the sensitivity is the same. We have also tested them without rinsing them and still the same.

DR. ENDERS: Without serum can you keep your bottles as long as--

DR. HULL: I haven't tried. I would say no.

DR. ENDERS: You use serum in those?

DR. MC LEAN: We use serum. We have no trouble.

DR. BODIAN: This is with two percent cast and 199?

DR. [illegible]

DR. [illegible] The question of [illegible] was raised by Dr. Rosen. I wonder whether or not that information might be pertinent to the question of potency. Might you not have a problem there? I don't know. I am just asking as a question.

DR. BOZEMAN: Losses on virus, Dr. Salk, have been negligible.

DR. SALK: What kind of filtration system?

DR. BOZEMAN: We use six, and in many cases our after-filtration titer has been higher than the pre-titer, perhaps not significantly higher, but we have said that for practical purposes there was no loss.

DR. SHANNON: Now, as far as the Committee is concerned, we would like to reconvene in about an hour, 1:30. We will try to close up fairly promptly so you can catch early trains.

We do want to thank the representatives of the manufacturing houses for being with us. I do hope they will take our request seriously. Thanks very much.

(Whereupon the meeting recessed at 1:30 p. m.)

AFTERNOON SESSION

DR. SERRELL: Will the meeting please come to order? I thought this afternoon we might start off by having any additional little discussion you want to have right now about the data that was presented this morning.

Are there any questions or discussions?

Dr. Ward is still here from the Cutter Laboratory, and if there are any questions you want to ask him, or that he would like to bring up from any discussion that you want to have concerning the data this morning, go ahead, and then I will ask him to add anything or to ask us any questions he may want to, at which point I think we will excuse them and go into executive session for the rest of the afternoon.

Dr. Ward, are there some questions that you would like to ask?

DR. WARD: Yes, sir, if I might.

I was just looking at this thing, and wondering, just trying to cover all the points -- whether these cases which have come out of mass immunization programs, whether you people had the information with reference to whether these injections were given with single syringes and single needles, or whether these were, say, five c. c. syringes and a single needle?

I was just trying to get at that, so that we would have all the facts.

I am not sure that the answer would be of any significance,

but it might be.

In other words, I am assuming that the Idaho cases given were all injected on the same day, were mass injections; and the San Diego ones, I know were mass injections.

DR. SEBRELL: I do not know that we have that information. I will ask Dr. Seibert. He has just come in.

Do you know, Dr. Seibert, whether these were cases inoculated with the same needles, the same syringes, or something of that kind, or whether these were individual syringes?

DR. SEIBERT: The first report on the Pocatella range was that they were in the same classes. However, there is a year difference in age, and I think that would have to be investigated. I would be suspicious of that first report.

DR. SEBRELL: Yes.

DR. SEIBERT: There is no other indication that there was any other situation such as that.

DR. WARD: What I meant was, these are cases from a large number, and in injecting, say, on the eighteenth, say Case Fourteen, I am assuming that there were a large number of other children injected on the same day.

DR. SEIBERT: Yes.

DR. WARD: And I was just wondering whether these injections, whether each injection was given with a single syringe and needle, or whether it was a five c.c. syringe or what?

I am not sure the data would have any significance, if we

knew that, that it might complete something in the picture.

DR. FRANCIS: Do you know about California?

DR. WARD: No.

DR. FRANCIS: We might guess that they used multiple needles with syringes.

DR. SHANNON: The answer is, I think, that we don't have the information, sir.

DR. WARD: I thought we might just know that.

DR. SHANNON: I think we might add that to the facts that we collect, what happened in these areas.

DR. SMADEL: I would like to clarify my information on one point, both as respects Dr. Ward's experience, and then perhaps Dr. Workman can fill me in on the others.

That is, the amount of material that is cultured from the final trivalent vaccine, and your group uses twenty-five c. c.'s of vaccine in a given bottle, and it tests enough c.c.'s of that vaccine so that it fulfills the minimum requirement of one c.c. tested for each liter?

DR. WARD: Right.

DR. SMADEL: Now what is the final volume of the total trivalent batch so that we have some idea of how many c.c.'s of trivalent vaccine is cultured in bottles.

DR. WARD: Well, I don't recall, but I think in the majority of instances, and it shows on the protocols, that the lots -- there might be one here, and there might be another; I don't --

but I can't recall any below one hundred liters. If so, it is just a little below.

DR. SMADEL: Yes.

DR. WARD: And I don't think there are any over one hundred and fifty liters.

DR. SMADEL: And that would be, I gather, the experience of a number -- except, perhaps, Lilly, which is running four hundred liter lots, so that they would automatically test --

DR. WARD: No, they are running twelve hundred liters there.

DR. SMADEL: Twelve hundred. Three times four.

DR. WORKMAN: We have reviewed all of these carefully, and all have been within the requirements, that is, a sample of one liter, and again the same amount.

DR. SMADEL: But, Bill, my point is this, that if a given group is in the habit of making small lots, by meeting those minimum requirements, they will end up by testing from one hundred to one hundred and fifty c.c.'s by culture.

DR. WORKMAN: Sure.

DR. SMADEL: Whereas another company will end up testing twelve hundred c.c.'s.

DR. WORKMAN: Right. That is exactly what they have done.

DR. SMADEL: And is there a possibility that in some of the organizations where we, for manufacturing purposes, have rela-

tively small flasks, we are left with smaller amounts of tissue culture inoculum than we would like to have, but twelve hundred, I take it, is about the tops?

DR. WORKMAN: The largest I have heard of.

DR. SEBRELL: Dr. Eddy?

DR. EDDY: I would like to say that all I heard of last year was about twenty or forty c.c.'s for about one hundred and fifty liter lot.

VOICE: But that was in three different places.

DR. SHAUGHNESSY: I have just made a table on this on the basis of the information we have, just trying to correlate this, and it seems to me that those manufacturers which have stated that they have used a larger inoculae, per bottle, and more bottles, are the ones that are showing the highest rate of contamination here, whereas, on the other hand, two manufacturers indicating small inoculae per bottle, and a fair number of bottles -- eight and ten -- are the ones that are indicating a low percentage of contamination.

DR. SEBRELL: Dr. Murray?

DR. BODIAN: I don't see the correlation here.

It seems to me you are testing for concentration, and if your sample is comparable, why should that affect your rate of recovery?

DR. SMADEL: We are not testing for that, but for one infectious particle.

DR. BODIAN: Well, that is exactly why the minimum requirements are set up that way, so that every sampling of every lot, regardless of size, is comparable.

You see, you are testing exactly the same thing, but that is not true of the monkey test, but with the tissue culture test, I think it is as logical as anything I can think of. I can't see any other solution.

DR. SHAUGHNESSY: Well, I think that the amount of growth, or the possibility of getting growth, will depend on getting more than one virus particle into the same bottle. I am sure we know this from actual experiment.

DR. FRANCIS: In other words, if you could put the whole lot into a tissue culture, you might find something.

DR. SHAUGHNESSY: But with this, you will get more positives than if you spread them.

DR. WORKMAN: We realized this and discussed that at the time the minimum requirements were written, and at that time this seemed to be adequate, and if it isn't, it should be increased.

DR. SHAUGHNESSY: I think that is one phase of it, and the other phase is how much goes into a given container of tissue culture?

DR. BODIAN: Well, this is on the assumption that more than one infected particle is needed to inject the culture; that is what you are looking for, the infected particle, and

looking for it in the logical way.

DR. SHAUGHNESSY: Well, are you speaking now in terms of -- for this virus which has had anything done to it; I can assume that virus which has been hit with something --

DR. BODIAN: Needs two infected particles.

DR. SHAUGHNESSY: Yes, you have this with bacterial agents too.

DR. BODIAN: Well, for example?

DR. SHAUGHNESSY: Well, in any disinfection setup, I am sure there is plenty of data that if you have what is called stuntings you can do this, and reactivation phenomena, if you plant one M. L., you won't get growth, twenty M. L. per vessel, but fifty M. L. will give you growth.

DR. BODIAN: But this is a different problem, though.

DR. SHAUGHNESSY: In the same container, and I am testing those various amounts by adding more to them.

DR. SALK: We need to find the limits.

DR. BODIAN: But this is a totally different problem.

DR. FRANCIS: But what you are saying is this:

At the present time, you are taking a chance in a sample which is one in a thousand that you will find something that is there, and that is what it amounts to, isn't it?

DR. SHAUGHNESSY: Yes.

DR. FRANCIS: If you took ten per cent of the whole business, theoretically, if there was a chance there, you would

have ten times the chance of getting it, but you are still working on the reasonable basis of sampling to have anything left to use.

DR. SMADEL: Well, I started the argument.

The whole point I had in mind was very simply this: That if we are dealing with something of the order of three or four or five hundred c.c.'s as a sample for culture as a minimum, and then if there are larger lots than that, go back to one c.c., but if somebody comes along with five liters of the stuff, theoretically, he would only test five c.c.'s in the final batch, and I do not think five c.c.'s is adequate.

DR. FRANCIS: That is what we were discussing yesterday though.

DR. SMADEL: O. K.

DR. SEBRELL: Yes, I guess we will get to that, but let's stop this for the moment and go back to the Cutter problem while these gentlemen are here.

Are there any questions any of us would like to ask Dr. Ward?

(No response.)

All right, Dr. Ward, is there anything further that you would like to contribute here?

DR. WARD: No.

I might first add that I think it was covered already this morning that the majority of us feel, and I am sure I can speak

for all of us, on this, that this year's tissue culture safety test has been more severe and more precise than last year's, for what good that there was on the present problem.

DR. SEBRELL: Any further discussion now with Dr. Ward here?

If not, I would like to excuse Dr. Ward from the Committee so we can move into an executive session and discussion and reach our decisions.

The day is getting on. I know some of you have made plane reservations.

Dr. Smadel.

DR. SMADEL: Well, I would like to ask one question.

As a result of the discussion today by Hall, I believe it was, that the presence of the wild virus can interfere with the apparent usefulness of the tissue culture test to detect polio; do you subscribe to that idea, and is it -- if so, what do you think we can do about it?

DR. WARD: I do not know whether I can subscribe to that or not, because I don't have the experience as yet.

The only think I would say that can be done about it is, if you bump into wild virus, is some tissue culture safety test, and this situation is not at -- is to repeat the whole works until you get to the point where you haven't got wild virus. It seems to me like, otherwise, you get into a lot of fancy manipulations, which is, in turn, open to question.

DR. SHERWIN: Dr. Enders?

DR. ENDERS: Could I just ask, was there anything experienced by the other people this morning that suggested anything to you about your experiences that have thrown any light or suggested anything that might be done in a laboratory, that might have been done or omitted that gave any hint?

DR. WARD: No, Dr. Enders, I can't pick up any hint as to any past deficiency, other than, possibly, what Dr. Stimpert and Dr. McLean mentioned, the carrying on of the tissue safety test for a longer period of time, and now that certainly brings up something very interesting, and, of course, when you get to that point, why, you wonder, now is that the end point? Should you go further?

In other words, where do you stop?

We had, actually, for some period of time -- I don't think we had ever gone quite as far as they, apparently, but we had gone several days beyond the twenty-one day, because it looked as though we were picking up something right toward the end, but that was wild virus that was showing up, and you get disturbed and try and type, and it doesn't type, and you think you are missing, and in the meantime you hold on to everything and move along.

And so I would say that we have done -- to try and answer your question -- I think that about what everyone else has done, that you hit these perplexing problems. There is no answer.

You sit down and discuss it with your own people, and you make the best logical move to try and change something, and you study that situation.

DR. SEBRELL: Well, thank you very much.

DR. BODIAN: You mentioned cramped quarters this morning. Do you feel that that is a handicap in any way?

DR. WARD: The only time that I have felt that we had our tissue culture safety test quarters relatively close to live virus, and I felt that they had given us some false positives, and hence that one earlier phase that we may have had an unusual number of false positives.

Now that was in a separate room all by itself, so I don't think it would have done anything, as far as I could see, but to gum up the test record maybe.

DR. ENDERS: The final bottling and all -- is that close to where the test is?

DR. WARD: The final bottling is done in the same place, which is entirely out and away from the polio virus quarters, and those are closed quarters, and those people wear special gowns, and they don't go out of those quarters without removing those, and there is no change-over in personnel, and so on there.

DR. ENDERS: The inactivation is done, also separate from where the virus is grown in the test tube?

DR. WARD: Well, it is done in an incubator in a closed

container, and then the final closed container moves on out of there.

So I don't think that I can visualize a potential of air contamination.

We actually did, when we were having some of these problems which the others have had, we have tried to, say, pick up polio virus by various air sampling techniques, and we have been unable to, because there is, of course, no information backward on carrying out this sort of virus operation on what you can get.

DR. SEBRELL: Well, thank you very much, Dr. Ward and Dr. Houlihan.

We appreciate your help.

DR. WARD: Thank you.

(Dr. Ward and Dr. Houlihan leave the room.)

EXECUTIVE SESSION

DR. SEBRELL: Now, gentlemen, I propose, in order to get along as quickly as possible, we have some typewritten pieces of paper here that represent an attempt to summarize what we did yesterday.

If we could distribute these and have you go over and modify it in the light of what we heard this morning, maybe we can button this meeting up without too much delay, because some of us are having to leave fairly early, and we want the benefit of all the advice we can get.

Have these been distributed, Mr. Fletcher?

MR. FLETCHER: I have to apologize for the limited number of copies.

DR. SEBRELL: I will have to ask you to look at them together.

(Copies are distributed.)

DR. SEBRELL: See that the Committee members get them, please.

MR. FLETCHER: Some more are coming up. I will have some more in just a minute or two -- in two or three minutes for you.

DR. SEBRELL: We will have some more copies in a little bit, but let us start with this one.

The first paragraph:

"The Committee agrees --"

And I think as we go through this, we will answer the questions that we had left over from yesterday, and when we have finished this document, if we have discussed it out, we should have the end of the Committee meeting, with all of the recommendations.

The first paragraph:

"The Committee agrees that the data presented this morning on reported cases of paralysis following innoculation with poliomyelitis vaccine manufactured by the Cutter Laboratories justifiy suspicion of a relationship

between inoculation with this product and the development of paralysis -- enough to have warranted the action taken in discontinuing the use of Cutter vaccine pending necessary investigations."

Is there anyone who disagrees with that, or wants to reword it?

DR. SMADEL: Well, I brought up this, that my inclination would be at the end of the word "justify" on the third line to delete down to the end of the "action" and say that the Cutter Laboratories was justified in this, because I think you are slapping them more than you need to slap them.

The only thing we want to take, is that we think the action was justified.

DR. HAAS: Yes.

DR. SMADEL: And we still think so, and we think it was justified, and that was the end of it.

DR. SALK: I second that. I suggested that yesterday.

DR. SMADEL: This --

DR. BODIAN: But isn't this the Surgeon General, instead of the press, getting this?

DR. SEBRELL: Well, I told you yesterday that when you hand it to the Surgeon General, then you just don't know. It is his then.

Off the record.

(Discussion off the record.)

DR. HAMMON: Then I think, in view of what you have said, that we had better go back and take another look at it now, because yesterday afternoon we were talking to the Surgeon General, and not for any other purpose.

DR. SEBRELL: All right. Would you want to --

DR. SALK: Start at the beginning.

DR. SEBRELL: Would you want to follow his suggestion there?

DR. SMADEL: The sentence would then read, delete "suspicion and end with "warranted".

DR. SEBRELL: Delete "suspicion" and end with "warranted" then?

DR. SMADEL: Yes.

DR. SALK: Delete "this morning".

DR. SEBRELL: Delete "this morning"; yes. Is everyone agreed to this change?

DR. SALK: Yes.

DR. HAMMON: I hate to disagree, but we thought yesterday that more could be in this if that was left in. You could read anything into that the way it is, and it maligns Cutter Laboratories less by qualifying.

DR. BODIAN: Well, the next paragraph merely is to explain the first.

DR. SEBRELL: The next paragraph then:

"The Committee understands that its primary mission

is to suggest studies to determine which of the following three possible explanations is applicable to the data as presented:

(1) Is this merely the coincidental appearance of poliomyelitis among people who happen to have been inoculated?

(2) Could the injection of the vaccine in some way have provoked the appearance of paralysis in a manner similar to the provoking effect that has been observed after use of other immunizing agents?

(3) Was the virus introduced by the inoculated vaccine?"

DR. MC GINNIS: May we say "Was a virus introduced"?

DR. SEBRELL: Now do you want to delete as Dr. Smadel suggested or not?

DR. BODIAN: I think so.

DR. SEBRELL: You would vote for deletion. You would, and you would.

Everybody but Hammon would delete.

Hammon, are you willing to go along?

DR. HAMMON: I am willing to go along.

DR. ENDERS: Could I suggest that we substitute the word "inoculation" by "injection"?

DR. SEBRELL: Where is that?

DR. ENDERS: In the second line.

DR. SEBRELL: In the second line, "following injection"?

DR. ENDERS: Yes.

DR. SEBRELL: In the second line to substitute the word "injection" for the word "inoculation". Done. "Following injection with poliomyelitis vaccine".

DR. ENDERS: Instead of "inoculation".

DR. SEBRELL: It sounds a little better.

Now the second paragraph, then; are you -- are there any suggested changes down through item one, two, three, as I named them?

"Was a virus introduced by the inoculated vaccine?"

DR. SALK: "Injected vaccine."

DR. SEBRELL: "Injected vaccine."

DR. FRANCIS: Well, presumably, you are injecting an inactivated virus, and should you say "Was a live virus introduced by the inoculated vaccine?"

Do you want to go that far?

DR. SEBRELL: All right.

"Was a live virus introduced by the injected vaccine?"

DR. SHAUGHNESSY: A good point.

DR. SEBRELL: Any further suggestions? Do you agree with this?

(Laughter.)

DR. SEBRELL: Well, maybe it is a wild virus.

The next one:

"The group recognizes that the incidence of poliomyelitis across the country in the next several weeks will shed a great deal of light on these questions. However, it feels studies of the kind contemplated above must be made in any case."

DR. SALK: The word "contemplated" doesn't seem to be related to anything.

DR. SEBRELL: Leave it out.

DR. SALK: Well, leave out the "above".

DR. SEBRELL: "Of the kind contemplated" -- all right -- 'must be made in any case."

"Across the country" -- "the incidence of poliomyelitis across the country" -- "throughout the country" is proposed.

DR. BODIAN: It isn't "throughout", is it.

DR. SEBRELL: I don't know. Pick a word.

DR. SALK: Well, I would say "The incidence of poliomyelitis in the next several weeks" without specification.

DR. SEBRELL: All right, "the incidence of poliomyelitis in the next several weeks" without specification; leave out 'across", "throughout the country".

DR. SHANNON: Well, if you are going to change that, "the incidence and distribution of poliomyelitis".

DR. SEBRELL: "The incidence and distribution of polio-

myelitis.'

The group recognizes that the incidence and distribution of poliomyelitis in the next several weeks will shed a great deal of light on these questions. However, it feels studies of the kind contemplated must be made in any case."

Is that satisfactory?

DR. SMADEL: I don't like the second sentence. I would like to suggest that the second sentence read, "It believes that careful epidemiological and laboratory studies must be undertaken."

DR. SALK: Good.

DR. SEBRELL: All right, instead of "feels studies".

"However, it believes --"

DR. SMADEL: "It believes that careful epidemiological and laboratory studies must be undertaken."

DR. SEBRELL: All right. "It believes that careful epidemiological and laboratory studies must be undertaken".

That is much more specific.

DR. FRANCIS: Now they have already been undertaken. Should they be continued?

DR. SALK: Be extended.

DR. SEBRELL: "Be continued and extended"?

DR. SMADEL: Yes.

DR. SEBRELL: All right.

Now it reads:

"The group recognizes that the incidence and distribution of poliomyelitis in the next several weeks will shed a great deal of light on these questions. However, it believes that careful epidemiologic and laboratory studies must be continued and extended."

Right?

DR. SALK: Yes.

DR. SEBRELL: O.K.

Next paragraph:

'The Committee believes that the failure of significant numbers of cases to occur following the administration of vaccine prepared by manufacturers other than Cutter warrants the continuation of vaccination with products prepared by the other manufacturers. It is possible, of course, that this recommendation may have to be modified in the light of the polio incidence data received during the next several weeks."

DR. SALK: I would like to suggest, Dr. Sebrell, "The Committee believes that the absence of significant numbers of cases following".

Take out "failure" "to occur".

DR. SEBRELL: "That the absence of significant numbers of cases".

DR. SALK: You see, we do not know whether they will or will not occur.

DR. HAMMON: The localization.

DR. SEBRELL: "That the absence of significant numbers of cases".

DR. SALK: Well, how can you have localization? You don't have anything to localize.

DR. HAMMON: Well, we have three cases, don't we?

DR. SALK: Well, the word "significant" covers it, I think, adequately.

Also, the last sentence might be changed to "The situation will be kept under daily review" or "should be kept under daily review", which is obvious now, and without saying that this is possible this might have to be modified, because that just sounds a bit weak and indecisive and a little tenuous.

DR. ENDERS: I would want to make this a little stronger.

DR. SALK: What?

DR. ENDERS: Should a significant number of cases occur with vaccine made by another manufacturer immediately.

DR. SEBRELL: "Suspension" -- is that what you had in mind?

DR. ENDERS: That is really what I had in mind, because if a number of these cases occur with another manufacturer other than this, I am sure I would vote that way.

DR. SALK: Well, you are making a decision in advance. You are crossing a bridge.

DR. FRANCIS: But we are to be quoted, apparently, and under

those circumstances we have to make sure that we are not so stupid not to have some thought that this might occur, and we ought to have some comment about it.

DR. ENDERS: It ought to be that we are aware of this possibility, and we are alerted to it, and should it occur --

DR. SEBRELL: Dr. Bell?

DR. BELL: I object to the reasons given in this first setence here. We do not know that enough vaccine has been given for these things to develop, and just say "to date we do not know" or "we have no evidence that there are cases following other lots of vaccine, and that we will determine that if an opportunity arises".

DR. SEBRELL: "To date we have no evidence --" What?

DR. HAAS: "That cases have followed --"

DR. SEBRELL: What?

DR. BELL: "Injection products of other manufacturers."

DR. FRANCIS: You have three right there.

DR. SEBRELL: "To date we have no evidence that significant numbers of cases have followed --"

DR. HAAS: "Injection."

DR. SEBRELL: "-- injection of vaccine made by other manufacturers".

DR. SHANNON: "Or have been associated with the injection", I think.

DR. BELL: "Thus the program will continue."

DR. SEBRELL: "Will have been associated" rather than "followed".

DR. SHANNON: Well, it is association with the vaccine.

DR. BELL: Well, if you don't think they are associated --

DR. BODIAN: Well, that is one of the possibilities being considered.

DR. SHAUGHNESSY: Doesn't this statement rather imply that we expect more to occur, though, and I don't think that is what we want to say at this time?

DR. SEBRELL: Well, if you take out the "to date", you then say "We have no evidence that significant numbers of cases have been associated with the vaccine made by other manufacturers therefore --"

DR. BODIAN: Well, is it significant that to date no cases have been reported?

Joe, you don't seem to think that it isn't.

DR. BELL: How much has been injected?

DR. BODIAN: Well, say --

DR. BELL: It has been long enough ago.

DR. SEBRELL: Well, he has some of the Cutter stuff in the same lots used in California?

DR. MC GINNIS: We have one hundred and ten thousand injected in Nevada, New Mexico, and Arizona, with no reported cases, and they were injected at about the same time. It began April 18.

DR. BELL: Cutter products?

DR. MC GINNIS: Yes.

DR. SEBRELL: And the same lot numbers as these that were used in California?

DR. MC GINNIS: Well, I can give it to you, and the dates these were shipped in here.

DR. SEBRELL: I don't see how we can lose on this.

DR. BODIAN: Now this may be, too; it seems to me that we have evidence that would not lead one to suppose that we could expect that kind of thing.

DR. BELL: Well, that is from the experience last year. They didn't have this trouble, apparently.

DR. BODIAN: But what about this year?

DR. SALK: It seems to me that what has been happening these last two days that there has been a tendency in people to arrive at a conclusion, and I will state for the record that I haven't decided in my own mind what the cause is, and those alternatives still stand.

But I think we have looked at the positive data, and we have not looked at all of the data, and until all of the facts have been analyzed, and to the same degree, we have to keep an open mind and say we just do not know.

DR. MC GINNIS: Dr. Sebrell, there have been 3,278,671 inoculated children in twenty-seven States. There are several others that I have not heard from yet.

DR. BODIAN: With other vaccine?

DR. MC GINNIS: With other vaccine.

DR. SHANNON: How many have been inoculated more than seven days?

That is the critical --

DR. MC GINNIS: I can give you the approximate dates with the numbers of the various States that have had vaccine on the fifteenth or sixteenth of April.

Now they started, all of the Southern States started the week of the eighteenth, and they all had Lilly vaccine, and I can give you the amounts in those States that have been inoculated.

DR. BODIAN: This is twelve days ago?

DR. MC GINNIS: Yes.

DR. BODIAN: How much?

DR. MC GINNIS: Alabama, 161,000; Arkansas, 83,900.

DR. BODIAN: How much?

DR. MC GINNIS: Eighty-three thousand, nine hundred; Florida, 164,000; Virginia, 180,000.

DR. FRANCIS: What was the one before Florida -- Arkansas?

DR. MC GINNIS: Virginia.

DR. SHANNON: I would like to point out that all of this is one batch of Lilly's, and I don't care if you had five million cases in one batch, you still wouldn't have any evidence pertinent to the question you are settling here.

Somebody told us last night that all of this was one batch to the Southern States.

DR. MURRAY: There was one lot of Lilly vaccine ready to go on the twelfth. The release of other vaccines was after that.

DR. MC GINNIS: There were no orders put out on the twelfth; the first was on the fifteenth.

DR. WORKMAN: Well, when was the second lot shipped?

DR. MC GINNIS: We shipped out everything they had by Saturday night, the sixteenth.

DR. SHANNON: What I had in mind is let's not neglect last year's experience and say that there is no doubt at all that you can inoculate large numbers of individuals with a vaccine of this sort and get no paralytic polio, and I think that if everybody hadn't been convinced of that, we wouldn't be here today, so to take one or two lots from one manufacturer, and an unknown -- to inoculate into an unknown number of children, and try to modify the generalities of the statement; it doesn't add up at all.

DR. BODIAN: Well, you have got a half a million right here.

DR. MC GINNIS: You hadn't gotten all of the States.

DR. BODIAN: It seems to me that we haven't got a good denominator, but then we haven't got a good numerator. I think we should look at it.

I think everybody is concerned to know whether the fundamental production of vaccine is shown to be unsafe, and it seems to me that that evidence could be refuted next week, but at the moment, it seems to me that the basic method of inactivation is satisfactory and there is no reason for general alarm.

DR. SEBRELL: Well, would you suggest a wording of this? Dr. Eddy, were you trying to say something?

DR. EDDY: Well, I was wondering, would you expect the same results from Lilly and Cutter, if this was due to live virus? What about the methialate? Would that affect it in any way?

DR. SALK: Dr. Eddy, if this was due to live virus, and that was what you just said, let us follow that; if you had an incubation period that short, and when you inoculate the monkeys and get this kind of thing, they are all down by the sixth or seventh day, and I think that the total pattern here certainly does not argue for live virus, unless you have another very peculiar kind of phenomenon.

DR. EDDY: Well, I was just pointing out that there is methialate in there, and I did experiments in our laboratory in which methialate does affect it.

DR. SALK: Well, you would expect quite a different pattern.

All I can say at the moment is that I just don't have enough evidence than to temporize and express the opinion that we just don't know.

DR. SALK: That's right.

I am just saying that, in case there is live virus in the Lilly and in the Cutter.

DR. SALK: Well, I don't like to make guesses, and suppositions on suppositions, and speculate on speculations.

DR. SEBRELL: Dr. Hammon.

DR. HAMMON: May I suggest a sentence to replace the first one?

DR. SEBRELL: "The Committee believes --"?

DR. HAMMON: Yes.

"Vaccines from other manufacturers have not come under suspicion; therefore we recommend continuation of vaccination with the products prepared by them."

DR. FRANCIS: May I read my version?

"The Committee points out that there is, to date, no association of cases significantly associated with the preparation of vaccine prepared by manufacturers other than Cutter, and it believes, therefore, that the continuation of vaccines and products of other manufacturers is warranted."

DR. SEBRELL: Well -- read it again then.

DR. FRANCIS: "The Committee points out that there is, to date, no association of cases significantly associated with the preparation of vaccine prepared by manufacturers other than Cutter, and it believes, therefore, that the continuation of vaccines and products of other manufacturers is warranted.

DR. SEBRELL: Would you buy that.

DR. ENDERS: I like that, except "significant".

DR. FRANCIS: There are three cases, but they are, apparently, not significantly associated.

DR. SALK: But doesn't that imply that there is a significant association, as far as the Cutter is concerned?

DR. FRANCIS: But I think that is what we have, a significant association there.

CHORUS: There is.

DR. FRANCIS: Yes.

DR. SALK: Fine, because the three alternatives are still there.

DR. SEBRELL: The three alternatives are still there.

DR. FRANCIS: And you are not saying which one it is.

DR. SEBRELL: Would that be acceptable to you, Dr. Bodian?

DR. BODIAN: She has got it down.

DR. SEBRELL: I am trying to keep a master copy here, but I lost track of it.

DR. ENDERS: Well, the recommendation is such at present.

DR. SEBRELL: Now we will read this once more so that you will hear it:

"The Committee points out that there is, to date, no information of cases significantly associated with the administering of vaccines prepared by manufacturers other

than Cutter. It believes, therefore, that continuation of vaccination with products of other manufacturers is warranted at present."

All right?

Now what about this second sentence? This is the first sentence at the top of page two on the copy you have. Do you want to delete that now?

"It is possible, of course, that this recommendation may have to be modified in the light of the polio incidence data received during the next several weeks."

DR. FRANCIS: I think, at least, that is the minimum.

DR. SEBRELL: You think we should have that?

DR. ENDERS: Yes.

DR. SEBRELL: All right.

DR. ENDERS: You could say that to begin with this recommendation would have to be modified.

DR. SEBRELL: And take out "It is possible, of course, that", and say that "This recommendation may have to be modified in the light of the polio incidence data received in the next couple of weeks."

DR. FRANCIS: Let us say that "in the light of the data regarding the polio incidence".

DR. SEBRELL: "In the light of the polio incidence during the next several weeks."

DR. SALK: "Incidence and distribution."

DR. SEBRELL: Incidence and distribution."

DR. BODIAN: He wants "data" removed.

DR. SALK: Take out "data".

DR. SEBRELL: "During the next several weeks". Take out "data received" and it says now:

"This recommendation may have to be modified in the light of the polio incidence and distribution during the next several weeks."

All right?

Now then, the next paragraph:

"The Committee, having divided itself --"

That sounds like an amoeba.

"-- into two groups to consider (a) poliomyelitis vaccine production, and (b) therapeutic and control measures, made the following specific recommendations to the Surgeon General of the U. S. Public Health Service."

DR. FRANCIS: Couldn't you say "makes"?

DR. SHAUGHNESSY: Since the whole Committee passed on all recommendations, is that about division necessary?

DR. SEBRELL: We don't need to say that. We can say:

"The Committee makes the following recommendations:"

We don't have to say what reproductive mechanism we went through.

DR. BODIAN: Do you need the two items?

DR. SEBRELL: All right. What is your wish now? I have

here:

"The Committee makes the following specific recommendations to the Surgeon General of the Public Health Service:"

DR. HAMMON: We have already made one. I think it should be "additional".

DR. SEBRELL: Yes, the first recommendation was general and these are rather specific things:

"That the number of monkeys used in the safety tests should be increased."

Do you want to delete that now today?

DR. HAMMON: I would just as soon see that deleted. I don't see the point of doing any bricklaying.

DR. SEBRELL: How do you feel about the monkey test?

DR. ENDERS: Willing to delete it.

DR. SEBRELL: You think eighteen monkeys is enough?

DR. HAMMON: The question is, is it too much?

DR. SEBRELL: Well, at least we don't want to reduce.

DR. BODIAN: Off the record.

(Discussion off the record.)

DR. SEBRELL: Now then, number two would become number one:

"That the manufacturers should be asked to submit more data pertaining to the virus inactivation curve -- at least five points being recommended on the curve, at least two of which should be in fairly close proximity to the ordinate

overshooting intervalon, and one on the minute."

DR. ENDERS: The truth of the matter is, they don't do it.

DR. SEBRELL: Apparently they are not paying much attention to it from the data we got this morning. I couldn't tell too well.

DR. BODIAN: We were looking for something down at the bottom there, which they obviously weren't paying attention to.

DR. SALK: It isn't so much that, but does it provide anyone else with confidence about the probable margin of safety?

DR. BODIAN: Can you tell by looking at the protocols that anything in there near the abscissa, does it tell you anything about the line they drew? The lines that Dr. Murray drew -- all the lines looked the same to me pretty much, and they are passed on the same points.

DR. SALK: Then I would say modify it in any way that would be in keeping with the purpose, if it is the purpose, of dividing some element with an idea of how things are going, so to speak, and what the presumed margin of safety might be.

DR. BODIAN: The impression that I got is that the present requirement is all right if you use a factor of four, instead of three.

DR. SEBRELL: Present requirements do not specify the factor.

DR. BODIAN: Oh, they don't? Well, where does that come

in?

DR. SALK: This is just a recommendation for guidance.

DR SEBRELL: Do you want to propose a recommendation for a factor?

DR. SALK: That is recommending control, which is what we did last year.

DR. SHAUGHNESSY: It seems to me the manufacturer would be spending his time more profitably to have a final safety test, rather than on the curve.

DR. SALK: Well, I think that the manufacturing procedure, itself, what I learned this morning, was something that Dr. Workman mentioned a year ago, and that is that he would pay more attention to the manufacturing procedure as a factor in safety. Now I will tell you quite frankly that the whole purpose in this line was to control just that factor.

And I think we learned this morning that when agitation, where we actually had to go to straighten them out, and Parke Davis indicated, too, what happened, that they tended to get into the first order of process.

I almost wonder whether it wouldn't be profitable to consider, as a recommendation from this Committee, that these laboratories be visited by a competent group who could go over this procedure with them as a means for enhancing the safety factor in that area, and this is all connected with this line and what you do with it.

(Discussion off the record.)

DR. SAR: Isn't this in the same category as some of these other things which will probably be considered by a a smaller group at a later time in connection with the old matter of the specifications and requirements?

DR. SEBRELL: You could well make one of your recommendations, if you feel so inclined, that we should appoint a small group to study and make recommendations on all the details of manufacture or something of that kind. Then I will have to appoint another little committee to do this.

DR. HAAS: I think this has a very definitive bearing on this problem--to ask the manufacturer his opinion, or after consideration of his data, after termination of his safety tests, was there anything different in that lot as compared to those lots which show nothing. I realize your theoretical point, Jonas. I am thinking now of manufacturing control. I hate to ask that the group recommend to a group of manufacturers the undertaking of an amount of control work that might, to some even small extent, take away some of the facilities that might be utilized to a more effective degree at some other place in the process. Now, if you change the better outfits--and I think Parke-Davis data were about as clean-cut as you can get--some of the others were very clean-cut--and ask them what they used in inactivation, a form they have not developed in their size kettles and their type of control, that type of inactivation, what they have come to expect as normal

2 inactivation curves against time, the clue they get out of inactivations, is this batch going as usual or is it abnormal-- it seems to me if you try to read more into this inactivation than this, you are making a very serious error.

DR. SALK: I agree with that. It's merely a safeguard and precaution that things are going reasonably well, and if it can be streamlined, as it obviously can be from the data presented today, I think the minimum requirements as stated right now would be adequate.

DR. BODIAN: Shouldn't one recommend, however, the 20-day bottles and the four-time factor possibly?

DR. SALK: These are the things I think ought to be considered in detail by another group.

DR. SHAUGHNESSY: I think Dr. Sebrell had a very good point when he suggested that we might recommend the appointment of a smaller committee to go over the specifications in detail. We cannot begin to do it here today.

DR. SEBRELL: I imagine this would be a job of a couple days itself, to go into each one of these little items. It might even require visiting the plants by a group of that kind to get all of the feelings on it.

DR. ENDERS: We visualized that possibility in our group discussion. I think I brought that suggestion out.

DR. WORKMAN: Dr. Sebrell, I would like to make one general comment. I doubt if the group here realizes the testing cost

specified with medium. I have no figures, but I guess they are on the same order as the active cost of manufacture, so far as polio vaccine is concerned. Now, to require testing which is not significant and does not bring in worthwhile information is very demoralizing, indeed; but the manufacturers feel with other more appropriate tests they could get much more information for the same amount of money.

DR. BODIAN: That's where I brought in the four-times factor. If they eventually do that and find they have to put it back in the cooker more days, after twenty-eight, it's kind of silly. Why not make it four?

DR. SALK: They are doing this anyway. You don't have to recommend it.

DR. SEBRELL: The manufacturers should be asked to submit complete data concerning virus inactivation.

DR. SALK: Dr. McGinnis, this is available on all the material that goes to Dr. Workman, and Dr. Workman has that now.

DR. FRANCIS: Is the alternative to cut that out entirely?

DR. SALK: Yes, until we have a chance to review this with them.

DR. FRANCIS: Take out Item 2 completely?

DR. SEBRELL: Take it out completely, and, as Dr. Enders has suggested, you might want to put in a general recommendation there that a small expert committee be appointed to make careful study and make recommendations concerning all the details of

vaccine processing.

DR. BODIAN: Refinement of methods.

DR. SALK: And testing.

DR. SEBRELL: And testing.

DR. ENDERS: Review the minimum requirements and make recommendations.

DR. SEBRELL: A small expert committee be appointed to review the minimum requirements.

DR. HAAS: I suggest that committee be appointed to advise the Director of N. I. H. regarding any changes to be made.

DR. SEBRELL: This is to the Surgeon General.

DR. HAAS: I know, but we want to handle that committee in terms of recommendations.

DR. SEBRELL: Well, they are recommending to the Surgeon General. Then he can delegate it to me if he wants to, or give it to somebody else.

DR. HAAS: O. K.

DR. ENDERS: That is agreeable to you, Dr. Workman?

DR. SEBRELL: Now, we have no record of the recommendation. I wonder if we can get it worded now?

DR. SHANNON: A small technical committee be appointed.

DR. SEBRELL: A technical committee of experts.

DR. SHANNON: To review minimum requirements in regard to refinement of methods of inactivation and testing.

DR. SEBRELL: That would be constituted for item 2, now. Do you agree to that?

DR. SNADER: I would like to see a little more diplomatic wording of that to determine whether changes are indicated. That implies you are going to start with an action right now.

DR. SEBRELL: Let's make it study the requirements and determine whether--

Now read what you have and let's see what we have.

DR. ENDERS: That a small technical committee of experts be appointed to study the minimum requirements with regard to refinement of methods of inactivation and testing to determine whether changes are indicated.

DR. SEBRELL: To study the minimum requirements to determine whether changes are indicated in methods of inactivation and testing. It's just a little out of order there.

To study and determine whether changes are necessary.

DR. WORKMAN: Dr. Sebrell, would the committee accept a suggestion to make recommendations, or are they actually going to make these changes?

DR. SEBRELL: And to make recommendations to the Surgeon General as to whether changes are indicated. To study and to make recommendations to the Surgeon General as to whether changes are necessary or indicated. The committee wouldn't have the power to make the changed. The Surgeon General would have to legally make the changes, so the committee would recommend to it.

All right. Number 3: "That the cooperation of the manufacturers should be enlisted in securing data on lots of material that for whatever reasons did not measure up to the manufacturer's own specifications and so were never submitted for approval, or on which information hitherto has not been made available to the Laboratory of Biologics Control. It is felt that this information may prove of value to the Public Health Service in maintaining continuous knowledge of potential difficulties in the manufacturing processes."

We are looking at these in the light of whether you want to delete these. They gave us all the data they had, except for Cutter, I guess.

DR. BODIAN: I think that is replaced by this Number 1, because this comes into the testing recommendations. We have the data now, and the question then is what to do with it; so I think that comes in Number 1.

DR. SEBRELL: We'll put it under Number 1 and delete Number 3.

DR. SHAUGHNESSY: That will mean in the future such information will not be submitted routinely.

DR. HAAS: Yes, we have to change the tense here, but that is the idea.

DR. BODIAN: They should continue to submit. They have already submitted some.

DR. FRANCIS: Say "do" instead of "did."

DR. SEBRELL: That the cooperation of the manufacturers should be enlisted in securing data on lots of material that for whatever reasons do not--

DR. FRANCIS: For any reasons do not measure up and so are not submitted for approval, or on which information hitherto has not been made available--normally would not be made available.

DR. ENDERS: Would not be made available routinely.

DR. SEBRELL: Routinely would not be made available. It is felt that this information may prove of value to the Public Health Service in maintaining continuous knowledge of potential difficulties in the manufacturing processes.

Now are you satisfied with that then?

DR. BODIAN: Did you get the word "continuing" in there?

DR. SEBRELL: The last sentence would be as it is written now--"in maintaining continuous knowledge."

DR. BODIAN: Oh, I see. The first sentence says it should be enlisted. Well, it has already been enlisted because they gave information this morning. I wonder whether the word "continue" there would not be more appropriate? Should be enlisted in continuing to provide data.

DR. SEBRELL: Now it would read, as I have that: "That the cooperation of the manufacturers should be enlisted in continuing to provide data on lots of material that for any reasons do not measure up to the manufacturer's own specifications and so are not submitted for approval or on which information

routinely would not be made available to the Laboratory of Biologics Control. It is felt that this information may prove of value to the Public Health Service in maintaining continuous knowledge of potential difficulties in the manufacturing processes."

DR. EDDY: I was thinking what this would do to their research program. Should you distinguish between their experimental lots and production lots?

DR. WORKMAN: Production lots. This should be limited to production lots.

DR. SEBRELL: On production lots of material. Number 4, then: "That every effort be exerted to stay abreast, on a day-to-day basis, of the current incidence of poliomyelitis among those individuals who have received the Cutter vaccine--securing both medical and laboratory data on each case reported." Do you want to add "epidemiological" as well as medical? We want to secure epidemiological and laboratory information. We might say "securing all available data." Why should that be limited?

DR. SHANNON: There is immediate necessity for getting stuff on Cutter and continuing necessity to get it on a broader basis.

DR. SEBRELL: Number 9: "That it is particularly important that practicing physicians should be urged to keep careful data on all inoculations they administer, including manufacturer's

name, lot number, site of inoculation, and general health of the individual at the time. The broad epidemiological study now under way to which this is related should concentrate on the early, pre-epidemic season in order that the data obtained will be helpful in making decisions on the current situation that can be made only on the basis of accurate and prompt statistics. In addition to epidemiological and physical data, it is recommended that laboratory studies be conducted on affected individuals and their families. It is recognized that this will mean a severe strain on laboratory facilities of the Public Health Service, and that other resources be enlisted in this laboratory effort through the sectional research program, the 24 cooperating laboratories under the Francis Study, etc."

There's the big general shot. Now you want to try to combine 4 with 9?

DR. SALK: Take 4 out altogether.

DR. BODIAN: That's really 3 at the moment.

DR. SALK: I agree with John--not only in regard to vaccinated children but also the non-vaccinated.

DR. SEBRELL: You think it is all covered under 9 and delete 4?

DR. ENDERS: 4 will be done anyway.

DR. BODIAN: 4 is in 9 now.

DR. SEBRELL: Yes, 9 covers the whole business. You can be sure that 4 is going to be done.

Number 5: "That very serious consideration be given to the matter of independent testing of each batch of vaccine submitted for approval." This was where we were talking about monkeys yesterday especially.

DR. BODIAN: I would go along with tissue culture on that kind of recommendation. The problem there is the preservative will make that difficult to do.

DR. HAAS: I have a question here of this order: We have already recommended a committee be set up to advise on minimum requirements. Isn't this superfluous?

DR. SEBRELL: Do you want to make this part of the responsibility of the minimal requirement committee? All right. We will delete 5.

Number 6: "That the Surgeon General should not advise the use of gamma globulin in the present situation; however, gamma globulin may be useful if it can be given within three days of injection, with a dosage of 0.2 cc per pound of body weight." Now this is a little matter of your telling a certain gentleman he should not advise. He should advise against, shouldn't he, instead of "he should not advise"? The Surgeon General should advise against the use of gamma globulin.

Do you agree with the gamma globulin recommendation?

DR. SMADEL: However, does the present situation--is that the 13 cases listed, or is this next week? That's the point I'm not clear on.

DR. SEBRELL: As I remember the discussion yesterday, the general idea is, unless you can give it within three days of the injection, it isn't going to do any good. The present situation has already passed that, and so you put in here a word indicating to the effect if there is a situation where you can give it within three days, you are to give it.

DR. BODIAN: You see, the Cutter situation is passed, because they stopped it three or four days ago.

DR. ENDERS: We have taken out all mention of Cutter here, so this doesn't have much significant.

DR. SHAUGHNESSY: I think it was put in there on the supposition that other products might be indicated.

DR. SEBRELL: I believe so. There is a possibility that something will happen with another manufacturer's vaccine in the next few days, and the Surgeon General would have this recommendation then to get out with right quick, although it seems to me the possibilities of catching him within three days are going to be very small. By the time you know you've got something, it will be more than three days before you can get any word back.

DR. HAAS: However, it may be helpful to him to have this.

DR. SEBRELL: It may be moral backing of some kind. People want to do something.

DR. MCGINNIS: Remember this vaccine has been given in 33 states. We don't know where it all went as a matter of fact. Are they going to distinguish between Cutter and some other kinds

of vaccine? If that recommendation got out, it could be implied that everybody who got the vaccine within the last three days should go out and get gamma globulin.

DR. BODIAN: Unfortunately, Bill Hammon has left.

DR. SEBRELL: He had to catch a plane.

DR. BODIAN: I don't know. I think not much harm would come from advising against the use of gamma globulin.

DR. SEBRELL: And say the Surgeon General should advise against the use of gamma globulin?

DR. BODIAN: I hate to recommend that strongly because the people who have been in favor of this have left.

DR. ENDERS: How about the "unrestricted use of gamma globulin," or some kind of qualifying word there? Or "It is the opinion of the committee that gamma globulin given after three days of exposure is of no value"?

DR. BODIAN: It's only the withdrawn lots you have to worry about.

DR. HAAS: That answers the question if someone asks the Surgeon General, "What do we do about gamma globulin?"

DR. BODIAN: You have to withdraw the lots before they get worried about it.

DR. SHAUGHNESSY: Some might have been given before the lot came under suspicion. I think the real quandary there is that this does not relate to any specific product. As McGinnis says, it could be interpreted to mean anybody's vaccine at any time.

DR. SMADEL: May I try this one: "The Committee suggests to the Surgeon General that gamma globulin has no protective value in the type of problem under discussion." No practical value--excuse me. No practical value in the type of problem under discussion.

DR. SHAUGHNESSY: Do you want to leave out "unless it can be given within three days"?

DR. SMADEL: We have just agreed that we can't do it.

DR. SEBRELL: What's the latest proposal now?

DR. SHAUGHNESSY: I think it's one of the minor recommendations.

DR. SEBRELL: Well, it is. But it has taken a lot of time.

DR. SHAUGHNESSY: I think we ought to get to some of the others which may be of more importance.

DR. SMADEL: All right. I'll read this one: "The Committee suggests to the Surgeon General that gamma globulin has no practical application in the type of problem under discussion."

DR. SEBRELL: Would you buy that now? And you say nothing about anything else. All right.

The next one: "That during the period of investigation of these cases, the Surgeon General might advise physicians and health officers that children receiving the Cutter vaccine should observe the usual precautions that are taken when the polio season is at its peak--avoidance of undue exercise, elective inoculations or surgical procedures, dental surgery, or other traumatic experiences for a period of at least 30 days."

Why you say that the Surgeon General might advise. There was a feeling yesterday, as I understood it, that might be a kind of panic-producing thing and weasel wording was put in here so it would give him something if he wanted it, or he could hide with it if he wanted to hide.

He might advise physicians and general health officers, you see--not the general health officers.

DR. BODIAN: I think we were pretty tired when we revised this. Now it's too bad we are in a position of wanting to change some of these things with some of the other people not present.

DR. SHANNON: The main proponent was Hammon. He had with him Francis, who went along.

DR. BODIAN: Well, I agreed to it, not very wholeheartedly. I don't think it is very important.

DR. SHANNON: It will cause difficulty for a large number of families who will not know what vaccine their children had. The second thing is to what extent will this result in a limitation of the activity of children over this period of time? I think if it's impractical in the first sense to give notification to the ones involved and would probably result in nothing, then I think we are just talking for the record and accomplishing very little.

DR. BODIAN: I think it's just like the gamma globulin thing.

DR. SHANNON: This was my feeling yesterday, although I am sorry Bill Hammon was not here to rebut that.

15 DR. BELL: We know a lot of questions will come to the Surgeon General from the parents. We said it wouldn't be of value in this other situation. We are considering now if this were my child and I knew he received a product possibly infected, what would you do with my child? This is what we want them to do: Not receive a polio shot for another three weeks.

DR. SEBRELL: Well, that's not in here. That's another recommendation. Let's stick to this one now. We mentioned that further down, in Recommendation Number 8. Let's stick to the one in front of us.

DR. BELL: These are the things we would recommend for our own child. We don't think it's practical, but we agree, although it hasn't been announced to the public as a whole, there are the facts for the Surgeon General as to what he could say.

DR. SEBRELL: We might combine these two. Number 8 says: "That the Surgeon General should recommend to physicians and health officers that the next injection for children having received the Cutter vaccine should not be given in less than four weeks--but that the Committee feels this decision, if concurred in by the Surgeon General, should not be given broad public circulation."

One way to handle it would be to let it--

DR. SCHEELE: The intention of not giving broad circulation is very good, but the very moment you give it to physicians, people will know it came from here, even from this committee;

DR. SABIN: What is your conclusion from that? What is remarkable?

DR. BODIAN: I am saying you are not seeing paralytic polio.

DR. SABIN: Who is not seeing?

DR. BODIAN: Well, people who are examining the monkeys that are being put on tests.

DR. SABIN: That is just what we don't know about the lots that they don't send in, they don't report. That was part of our decision to ask them for the protocols of the lots which they don't send in.

DR. EDDY: I would suspect there aren't many lots because of the numbers that come to us.

DR. WORKMAN: I said a moment ago that is probably true, Dr. Eddy, but--

DR. HAMMON: At the risk of annoying you -- as I have said to a number of this group in the past several years, I still think we should perhaps give more real consideration to the possibility of adding one more test, and that is centrifugation of a few hundred cc's of this material. Objections were raised earlier that it used too much of the vaccine, that you throw too much away in the testing. Now big lots are made, and why can't one take 500 cc's and test the sediment in the tissue culture? It is a more extensive test of the living virus.

DR. EDDY: We did that the other day, but results aren't--

be asked to do evil to rule potential. There is an addition to paragraph 5: This interval would provide, in addition, better conditions for investigation of the cases involved."

It would provide some scientific justification, also, for withholding further inoculations for a period.

DR. SEBRELL: Well, you see, we discussed that yesterday, too, and this can be turned the other way to indicate that you are making guinea pigs out of these kids.

DR. SHANNON: The board is meeting again Wednesday, I believe. If there is not an unfavorable reaction from the group here, they will re-institute their plans.

DR. SCHEELE: One of the advantages of having some of these things done relatively publicly is that you get very wide dissemination, and you get uniformity of treatment of the problem. Probably the easiest way to get it to physicians who have kiddies they have injected.

DR. BODIAN: Including their own, and those of their physician friends, which is quite a common thing right now.

DR. SEBRELL: What action do you want to take now on Item 7? We haven't disposed of that yet.

DR. SHAUGHNESSY: It seems to me the recommendation is how can you get it to the people without causing panic?

DR. SEBRELL: Well, I don't think this committee has to decide that question.

DR. MCGINNIS: I think the committee might take into

consideration that through last Saturday, 6 million cc of vaccine had been shipped out.

DR. SEBRELL: This applies to the children receiving the Cutter vaccine.

DR. MCGINNIS: The point Dr. Shannon brought up was whether people would distinguish between the two.

DR. SHAUGHNESSY: I think in mass immunizations they'll know which they got. The health officers will broadcast that information and tell the people.

DR. SHANNON: You say you would have your child do this, Joe. Take the number of cases we have a month, forgetting now mechanics, there's probably one in 10,000. Now with those studies that have demonstrated an association with increase of attack with exercise, and the like, and a whole variety of other things, you have to scale that down from one in 10,000 by some other factor; and I wonder if you're not getting down to probabilities which are so low that in actual fact you wouldn't put your youngster, who had such exposure, under undue restriction of physical exercise. You wouldn't withhold dental surgery from the individual, if it seemsed indicated. I mean we are dealing with very low possibilities.

DR. BELL: I agree with that thoroughly. The provocative effect of these things is quite small, but here are children who have potentially received or possibly received virus injection. If it helps somebody to answer questions intelligently

DR. [illegible]: The first phrase, I think we thought, last night, was a satisfactory qualification--the immunizations with regard to the Cutter vaccine. This was only an interim recommendation, since we didn't know what the situation was. I don't know what the other people would feel about the force of that now. It seems to me this partial committee isn't really able to make a drastic revision when actually most of the members who were interested in this are not here. The thing is not very important either way in my mind.

DR. SEBRELL: It is a recommendation to the Surgeon General, though, anyhow. It says he might advise physicians and health officers. He'll do it or not as he wishes. This is something that would strengthen his hand if he wants to use it. If he thinks it inadvisable to use it, he can hide it.

DR. SCHEELE: This takes off, essentially, from the viewpoint that since we don't know whether there is live virus in the Cutter material, this is going to prevent additional provocation in those cases. There is the basic question of provocation all along the line with anybody's vaccine, and especially provocation as we have a lot more virusemia as we get toward the peak season.

Have you had any discussion whether we are going to suggest, also, we find some cut-off point for immunization moving toward the north area of the country, as we hit the peak season?

DR. ENDERS: Not exactly that way. We discussed the use in

epidemic.

DR. SCHEELE: It seems to me if we feel strongly about the kids who had Cutter vaccine, in the next four weeks--

DR. BODIAN: That was discussed very actively yesterday.

DR. SEBRELL: You want to let the item stand, then, if I understand the latest tenor of the committee?

Then let's look at Item 8: "That the Surgeon General should recommend to physicians and health officers that the next injection for children having received the Cutter vaccine should not be given in less than four weeks--but that the Committee feels this decision, if concurred in by the Surgeon General, should not be given broad public circulation."

DR. SCHEELE: Would you be willing to change the last clause and say that the Committee feels that if concurred in by the Surgeon General, this should be made known to medical and public health groups? Don't tell the public, but say the same thing in another way.

DR. SEBRELL: This should be made known to physicians and health officers. Would that do it? "That the Surgeon General should recommend to physicians and health officers" is what it says now. Why don't we just delete the last negative phrase? We'll stop at "Surgeon General."

DR. SCHEELE: I'm going to back off on you now and say--of course, the only place we can control broad public circulation is from the public health service, but maybe you still want to

keep it in because it is an additional recommendation. When you say "give it to physicians and health officers," that's two groups of people. That isn't saying "don't give it to the public," so maybe you still want to say it; so I'd like to back off on what I was recommending and let you reconsider it because you still may want to say it. It still adds something, you see. If it isn't there, you have stayed silent on the issue. It doesn't preclude our giving it to the public, you see.

DR. SEBRELL: All right. You want to leave it that he shouldn't give it to the public as we wrote it originally?

DR. ENDERS: There's no use stirring up more worry, and it doesn't really concern the public.

DR. SCHEELE: If we can spot all the Cutter vaccine, we can pass this word to every state health officer in a state which has had Cutter vaccine and just stop it that way.

DR. SEBRELL: I think that's what the committee had in mind.

Item 9, on the epidemiological study: "That it is particularly important that practicing physicians should be urged to keep careful data on all inoculations they administer, including manufacturer's name, lot number, site of inoculation, and general health of the individual at the time. The broad epidemiological study now under way to which this is related should concentrate on the early, pre-epidemic season in order that the data obtained will be helpful in making decisions on the current situation that can be made only on the basis of accurate and prompt statistics

In addition to epidemiological and physical data, it is recommended that laboratory studies be conducted on affected individuals and their families. It is recognized that this will mean a severe strain on laboratory facilities of the Public Health Service, and that other resources be enlisted in this laboratory effort through the sectional research program, the 24 cooperating laboratories under the Francis Study, etc."

Now, Dr. Francis, I thought, indicated his willingness to go along with this and I understood from Dr. Salk that the Polio Foundation would put up the money for Francis to do this, if he wanted to do it; and we would propose, through Haas, to activate the sectional laboratories and Dr. Haas and Dr. Shannon would probably get this going by Monday, I hope, to see what money they need, and that sort of thing.

DR. SCHEELE: Tom himself isn't anxious to be the center for developing this thing. I think he thinks that Alex and the overall surveillance program can build this in. Then it becomes a question of how many of the laboratories are needed, are still willing to work, and if there is any cost who pays for it.

DR. SHANNON: Dr. Scheele, we have had a chance to discuss this briefly with Dr. Haas. The proposal, as it now stands, is 1. one person be asked to accept responsibility for the program; 2. and it should involve the sectional research program, and Dr. Haas will contact the members there and tell them exactly what the job is and the extent to which it will attain; 3. He will

contact these members in Francis's 27 groups not obtained in the sectional research group. Actually there is a fair amount of overlap between the two groups. At a later time when it has been decided who will participate, then it will be operated under Vicks' laboratory or run it out of the Montgomery Laboratory under Schaeffer. We will have a specific proposal for you on Monday.

DR. SCHEELE: It seems to me the important key thing here is there were certain kinds of operations during the field trial. You did have state health departments cooperating and a lot of health departments cooperating, but the more responsibility we can assure the health officers in the states assuming, the better off we'll be. We have to get them to stand on their feet and not be cooperators in a great national testing program. This will give them the strength to be able to do these things, even without any Polio Foundation help or Public Health Service help to do their normal job. They have other things they are studying.

I think we should be sure, in this opportunity we have, that we build strength and build a better strength between our sectional laboratories. Let's assume we had an enemy attack. We're going to have to depend on states. They are going to be official agencies operating. If we can build the groups together as we go along in the next months ahead, and this will give us a basis for doing it, we are going to have a lot better integrated network of program. Then, as we get exotic diseases coming along,

which no one knows much about, we'll have a base to work from; instead of coming to Washington to work from one laboratory, we'll have islands of competence all over the country.

DR. ENDERS: One thing important is to get all the laboratories quickly lined up to receive materials and the Public Health people in the states to get them. Even if the laboratories can't work them all up right away, let's get them. In other words, a depository should be arranged for the collection of material.

DR. SEBRELL: That is under way already, Dr. Enders.

DR. MCGINNIS: I talked with Dr. Francis. He gave me the same attitude he gave you. As Dr. Van Riper said, the Foundation would be willing to cooperate any way possible. My suggestion here is to carry this plan in all of these laboratories at the present time. If I remember correctly, the National Foundation's appropriations go through June. It would be my suggestion that whoever in the Public Health Service is going to do this job immediately get in contact with Dr. Henry Coome, Director of Research in our laboratories, and handle these grants, because some of these men may have work to do that they would be reluctant to give up unless they had word from Dr. Coome that this took precedence.

DR. SCHEELE: You may not need as many laboratories in the period ahead.

DR. MCGINNIS: Dr. Coome could tell you what these laboratories could do in amounts, etc.

DR. [illegible]: [illegible] a tremendous volume of material.

DR. BOHAN: These laboratories in the vaccination program were geared to study serum from vaccinated individuals, not only cases. The cases represented the smaller load.

DR. SCHEELE: I hope there are a few people around who just as research projects are going to be studying what has happened to antibodies, too; but that is not our immediate problem.

DR. SEBRELL: Does anyone want to make any changes in Recommendation Number 9? Are you satisfied with it?

DR. SCHEELE: Incidentally, this program was announced by us a day ago and the bloods are being collected or have been collected on the bulk of these children by now.

DR. SEBRELL: Well, if there is no change in 9, let's look at 10: "That immunization against poliomyelitis should be carried out as far in advance of the epidemic period as possible and no special effort should be made to provide vaccine to those areas which are believed to have high epidemic prevalence. Therefore, it should not be necessary this year to make special stockpiles of vaccine for epidemic use."

DR. SMADEL: I have a notation here on Tommy Francis's copy, which he read to me before he left. I'm not quite sure I have the thing in the proper sequence. I will try it. It doesn't change the sense much. "That immunization against

poliomyelitis should be carried out as far as possible in advance of the epidemic period and this year vaccination should not be recommended in areas of high epidemic prevalence. Hence, no special efforts should be necessary this year to make special stockpiles of vaccine for epidemic use."

I don't see that that changes it a lot. It's the same thing.

DR. SHAUGHNESSY: He is confining it to this year.

DR. SEBRELL: We've got it this year, too. "Therefore, it should not be necessary this year to make special stockpiles of vaccine for epidemic use."

DR. BODIAN: He emphasized the negative aspect of not giving it during the epidemic.

DR. ENDERS: It seems to me you could almost interpret his as withholding it.

DR. SMADEL: I introduced it by saying that it wasn't quite clear.

DR. BODIAN: I like this one better. This was passed on by the whole committee last night.

DR. SEBRELL: We'll leave it as it is, then.

Number 11: "That continuing review should be made by a smaller unit of this Committee concerning the optimal route of inoculation with poliomyelitis vaccine--epidermal, subcutaneous, or intramuscular--in order to provide current information on how the inoculation route (and hence dosage) may pertain to

provocation, legislation, supply and allocation problems, and related matters.'

DR. SMADEL: It seems to me outside the purview of this particular committee.

DR. SCHEELE: We'd like very much to have this committee or a reconstituted committee, maybe a smaller one, advise on most of those things. Indirectly they are recommending on supply and allocation.

A week ago when we had the big technical group including manufacturers talk about supply and distribution problems, we got two recommendations; that is six members, but we got two that suggested setting up committees. Has there been discussion here of the distribution committee which has its first meeting Monday? If you have time, it might be worth knowing about, because all of you will be out on the firing line, and this may be helpful to you.

The distribution committee consists of nine people--AMA representative, state health officer, local health officer; Phelps is the general practice man and Barry is the pediatrician and Julian Price is the AMA person. He's also a pediatrician, incidentally. There are two PTAs--negro and white--Mrs. Leonard and Mrs. Williams, NFIP--Mr. O'Connor. We wanted to have, and the committee suggested we have someone from industry on, and we knew we couldn't have someone on--from one of the six drug firms, but tried to get someone from one of the two major drug

manufacturing associations; but this turned out to be as complicated as did the business of having a manufacturer, so there's a blank on that.

Then we have two people representing the pharmacy industry, this because we couldn't make a choice of one without having both, so we have American Pharmaceutical and someone who is an apothecary and has an ethical pharmacy at Saint Paul. That group will meet Monday and organize. It's their job to set up a pattern for distribution which would provide reasonable equity between the states. It was suggested that probably as simple a formula as they could have, recognizing you couldn't have a very perfect formula, might be to take the population between the ages of one and eighteen as the base. You would allocate to each state based on that. You might also skew, though, the population when the polio season was starting to peak.

Conceivably, when we are brave enough to want to do it, during epidemic periods, one might have an epidemic factor but you are recommending against that; and I think everyone today will accept that. Then the six firms will be given the blueprints of how each should ship his material to make up that mosaic of distribution to the states.

There is one other activity of the committee, but this is essentially being the post office, rather than one they have to make any decisions on. The committee hopes to receive from the states information on how the state then would like to

see the supply it will get distributed as between tax-supported programs and commercial sale. That will come to the committee to be passed back to industry, and from then on the drug firms are on their own. They'll ship into the state whatever--every one of them to a man has agreed to follow this quite explicitly.

This is all voluntary. We can't tell the industry what to do. We're not doing it under any law that says we can tell them, but they are all in short enough supply and worried enough and have been since each one discovered the other fellow didn't have too much, to be willing to have almost anything happen. So much of the success beyond that will depend on how the state can keep people happy on what is happening within the state, and this will not be a very satisfactory thing until the supply builds up, when there are only a few cc's to scatter around commercially; and that will continue for a while, as you know. Everyone will feel he should have had it if the fellow across the street had it.

We don't think an allocation program under law in the Public Health Service would be any more successful because we would still have the end problems, but a high degree of state planning is important; and within the community decisions will have to be taken as to what the age priority group will be. If there is to be a pattern, it will have to come under the state medical societies and local medical societies and some of those must be

public measures to help the material within the population group of the greatest risk. We know it will not work perfectly but again I don't know how you can release this unless you had 160,000 cops to stand alongside 160,000 physicians.

Quite a few state health officers are again seeing the tight supply situation, knowing the public pressure on them because of the tight supply situation, which reflects on them reflects on the Public Health Service, would like, if there were a possibility of changing the dose schedules or intervals between doses--would like to know at some early date what that change should be. They are all hoping there will be a change in that direction to spread the supply. I think we have to follow their recommendation. I think we should, from time to time, review any new data that come along. I suspect there isn't going to be much to review except possibly some of the greater detail which Jonas may be prepared to give in a few more days now. I understand he mentioned his paper.

DR. SEBRELL: Yes, he's giving a paper at nine o'clock Monday morning in Atlantic City.

DR. SCHEELE: It seems to me this might well be a look-over of that, and then one decides whether this is anything to move toward, and you have to have what I understand you talked about here--this is a bad time to change any dose schedule because of the furore that would cause; but we would like to have a committee to do it.

DR. SEGETLI: This would be in relation to supply and allocation, as it is put in here--". . . localization, supply and allocation problems, and related matters."

Would you be willing to let this stand, then, so this committee would help the Surgeon General in these things he has presented to you?

DR. SCHEELE: This supply and allocation on that committee could be advisory to the other committee that we referred to.

DR. BODIAN: It seems to me this is really a little bit outside of what we were called for, but it is very important. What impresses me, the point somebody is getting across here is this ought to be considered in relation to what we know. The fact is we usually don't know very much when we get together to discuss these things because we are waiting for one person to find out. I think an important recommendation is to get somebody else beside Jonas to work on developmental problems. Shouldn't there be a little stimulus elsewhere?

I'm not saying this because I think Jonas isn't doing a good job, but I think it would be a lot better if there were at least two groups working on development because they pertain to very important problems as to how far it will go, and provocations, and the like.

DR. SCHEELE: Did you consider the possibility that you, as a group, or this group reconstituted with any additions you might suggest, might be a semi-permanent committee to carry

on through the emergency period can be called from time to time by Dr. Sebrell and these things would be done by a subcommittee because we have four more cases in California that you haven't been told about. All Cutter. This is going to build up. It's going to build up on the cases that would have occurred anyway; and there will have to be continous consultation.

Heaven forbid that we have to get together and discuss something for other manufacturers in the same light we are discussing Cutter, now, but it does happen. You know you might get a call.

We have our mechanics of appointment all taken care of. The public will feel happy because they will feel there is something warm that exists. Meetings may be on an ad hoc basis. We may have to have a lot or may not have many; but we might appoint a committee so you don't all have to struggle on these things. Say on the dosage schedule thing, if a few of you--

DR. SEBRELL: I told them yesterday that while we had called them as an ad hoc committee, we hoped they would continue and they have already recommended the appointment of another subcommittee to look into minimum requirements. There will be a technical committee to look into the details of minimum requirements for processing and there would be another subcommittee to take up this aspect of it. If they were willing to continue, we would have a continuing committee to which subcommittees would work on detailed problems.

DR. SHAHULL: Doctor, before you leave, there is one little point about publicity. The last four lines indicate the committee hasn't attempted to screen their recommendations in the light of their possible professional or public use, but do any of you have any objections to anything we have put down here being made public with the restrictions you have written in, one or two items? I just want to be sure none of you has any reservations about the use the Surgeon General might make of this material with the little things you have written in in one or two places.

DR. SCHEELE: This isn't saying we will use it. We'll look at it very carefully after the meeting, but we do have a tough problem. We can't have much of a news brown-out. The American public is concerned. There is no basis even for sicentific discussion without the press being in.

DR. SHAUGHNESSY: There is one point, and I hope Bodian brings up a recommendation that he and Dr. Enders and Dr. Francis and I looked over. I'm sorry I can't be here for the discussion of it, but I am heartily in favor of it.

DR. SCHEELE: This morning we had a very bad reaction from the press. They had turned up out here and Jud Hardy was trying very hard to protect all of you and one of them took this as an effort to keep the public from knowing what was going on and called me and wanted to know if it was the policy of the Public Health Service and Mrs. Hobby and the President to have

a brown-out on this shot or that. He was just putting a sheet of paper in his typewriter to go ahead and blast us again for a brown-out.

We have been blasted, as you know, a week ago Friday because we didn't allow the press and public in. We were blasted on both sides. It's very hard to explain to them we like to have quiet and calm when we discuss these particular technical matters and we pulled out of it all right, I think, with this particular chap and I told him, Jud, that I thought you were--

MR. HARDY: I caught him with his head in the window there busily taking notes on what has been said. I ran him away.

DR. SCHEELE: Well, he had a right to be run away, but these fellows have got the upper hand which is why all of us can't operate normally now.

DR. BODIAN: I personally hope there will be a statement so I can refer people to it instead of saying that I can't say anything. I received a cable from Copenhagen during the meeting, "Please inform us cable collect about Cutter vaccine complications."

DR. SCHEELE: I had a long-distance call from Stockholm from the Health Officer of Sweden. They are going on 40,000 children on Monday. It is Swedish-produced vaccine, I think, in this case; and he wanted to know the story, and I said, "O. K. Go ahead."

DR. SCHEELE: Dr. Enders, Dr. Broughton, indicated you had something to introduce. I was going to ask as a final thing whether there was anything we overlooked of importance that any of you want to add here.

DR. BODIAN: Actually we talked about some things, I think, which were clarified by the morning meeting with the manufacturers' representatives. At least that was my impression. Most of them were covered by that.

DR. SCHEELE: After this meeting, we'll sit down and see what we can say. If any of you can stay, we'd welcome your staying and helping us. Beyond that, anything you give out as a press release, if you haven't stayed to the point that we have finished it, we sweat blood on these things--they're awfully hard to write--after our meeting Friday, it took from 4:30 to 10:30 to be satisfied with what we were saying. But we will send you telegrams to whatever address you tell us to send them, as soon as we have it for the press. They may catch you before you get home, or as you are leaving here; but then you will have it just practically as soon as the press does.

If you will give us the place where you would like it sent--

DR. ENDERS: We've agreed not to talk at all, but refer all questions to you.

DR. SCHEELE: You still might like to know exactly how we phrased it because you may extend that within certain limits

or probably I [illegible] "What does this mean.

DR. BODIAN: Most of the people I have talked with about this thing before this meeting wanted reassurance. That seemed to be the main thing. My own feeling is what I have heard within the last few days is more reassuring than I thought when I came here, particularly this morning, and that was really what we were getting at at breakfast, and I still feel that--I feel more strongly about it since this morning's session.

DR. SEBRELL: I want to give every one of you committee members a chance to add anything you want to say at this point.

DR. ENDERS: We had one point for the technical subcommittee I feel strongly about, and I know Shaughnessy does. That is Dr. Sabin's insistence on changing the Type 1 strain to one of low-grade pathogenicity as soon as possible and in the future manufacture of the vaccine. I can see no reason for running that added risk of including that highly--

DR. BODIAN: Well, John, the reason I didn't want to bring that up now is I think that would have been a subject for discussion because there are two sides to this.

DR. ENDERS: We can't do anything about that now anyway, but I think it's important for that subcommittee to leave it as a good piece of unfinished business.

DR. BODIAN: That is a problem that has been brought up during the last two years repeatedly.

DR. SEBRELL: Anyone else want to add anything or say

anything at this time? If not, I think we have reached a point where I want to extend to your our heartiest thanks and appreciation; and I know I am speaking for Dr. Scheele, as well as myself, and for Haas and Workman and all the rest of us here for coming here and helping us with this very difficult problem.

We really do appreciate the fine work you have given us here over the past couple days, and we will appoint this expert subcommittee that you have indicated right away, to go into the minimal requirements, and we will keep you informed about the progress of that.

(Whereupon, at 5:00 o'clock p.m., the meeting adjourned.)

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